(19)日本国特許庁（ＪＰ）　(12)**公開特許公報（Ａ）**　(11)特許出願公開番号

特開平10－180058

(43)公開日　平成10年(1998)７月７日

(51)Int.Cl.[6]	識別記号	ＦＩ
Ｂ０１Ｄ　69/08		Ｂ０１Ｄ　69/08
71/44		71/44
71/68		71/68
Ｄ０１Ｆ　1/08		Ｄ０１Ｆ　1/08
8/10		8/10　Ｚ

審査請求　未請求　請求項の数７　ＯＬ　（全 11 頁）

(21)出願番号　特願平8－343858

(22)出願日　平成８年(1996)12月24日

(71)出願人　000003160
東洋紡績株式会社
大阪府大阪市北区堂島浜２丁目２番８号

(72)発明者　加藤　典昭
滋賀県大津市堅田二丁目１番１号　東洋紡績株式会社総合研究所内

(72)発明者　塩田　裕啓
滋賀県大津市堅田二丁目１番１号　東洋紡績株式会社総合研究所内

(72)発明者　山本　勇
滋賀県大津市堅田二丁目１番１号　東洋紡績株式会社総合研究所内

(54)【発明の名称】　中空糸膜

(57)【要約】

【目的】　血液透析療法において透析合併症の改善を可能にするハイパフォーマンス型の透析膜において、血液へのエンドトキシンの侵入を実質的にゼロにすることにより、安全性と合併症の改善を向上させた血液浄化膜を提供すること。

【課題】　疎水性高分子よりなる中空糸型血液浄化器において、親水性高分子が、均一構造を有する膜内に存在し、エンドトキシンに対する吸着性を有し実質的にエンドトキシンを通過させず安全性の向上したことを特徴とする中空糸型血液浄化膜であり、低分子タンパクであるβ2-ミクログロブリンを５０％以上の透過性を有することを特徴とする。

【解決手段】　β2-ミクログロブリンの５０％以上の高い透過性能を有する血液浄化膜において、エンドトキシンに対する高い吸着性と除去性を獲得することができ、血液透析等の医療分野でより安全性の高い治療が可能となり、今後、透析合併症への改善を新たな指標から開拓する血液浄化膜としてその利用が大いに期待される。

【特許請求の範囲】

【請求項１】　中空糸膜を構成する全（球水性及び親水性）高分子に対する親水性高分子の含有率が５～２０重量%、球水性高分子の含有率が９５～８０重量%である中空糸膜であって、該中空糸膜の内表面、外表面及び膜中間部における親水性高分子の含有率（内表面がA%、外表面がB%、膜中間部がC%）が下記の式を満たすことを特徴とする中空糸膜。

（（A－X）^{2}＋（B－X）^{2}＋（C－X）^{2}）０．５／X≦０．５

但し、X＝（A＋B＋C）／３

【請求項２】　前記中空糸膜の膜断面を３００倍の電子顕微鏡で観察するとき、明らかに認められるボイドまたは網目構造が存在せず、前記中空糸膜の内部構造が実質的に均一構造であることを特徴とする請求項１に記載の中空糸膜。

【請求項３】　前記中空糸膜の内表面及び外表面を５００倍の電子顕微鏡で観察するとき、明らかに認められる孔が存在せず、前記中空糸膜の表面構造が実質的に平滑構造であることを特徴とする請求項１又は２に記載の中空糸膜。

【請求項４】　前記中空糸膜を充填した内表面積換算の膜面積が１m^2 のモジュールにヘマトクリット３０%、蛋白質濃度７g／ｍｌの牛血液を流速２００ｍｌ／分で流し、濾過流速１０ｍｌ／分で濾過を行った時の、牛血液中のβ2-ミクログロブリンの篩い係数が５０%以上であることを特徴とする請求項１乃至３に記載の中空糸膜。

【請求項５】　前記疎水性高分子が芳香族ポリスルホン系高分子であることを特徴とする請求項１乃至４に記載の中空糸膜。

【請求項６】　前記親水性高分子がポリビニルピロリドンであることを特徴とする請求項１乃至５に記載の中空糸膜。

【請求項７】　前記中空糸膜が膜構造保持剤として多価アルコールを含むことを特徴とする特許請求項１乃至６に記載の中空糸膜。

【発明の詳細な説明】

【０００１】

【発明の属する技術分野】本発明は、人工臓器として血液浄化等に用いられる中空糸膜に関する。さらに詳しくは、血液浄化等において、β2-ミクログロブリン等の低分子蛋白質の高い除去性能を維持しつつ、透析液側にエンドトキシンが含まれる場合にも、そのエンドトキシンを実質的に血液側に侵入させることがない中空糸膜に関する。

【０００２】

【従来の技術】従来から、医療分野においては、血液中の老廃物を除去する目的でセルロース、酢酸セルロース、ポリメチルメタクリレート、ポリアクリロニトリル等の重合体を用いた透析膜や限外濾過膜が用いられている。特にセルロース膜は、腎不全患者の延命・社会復帰の為の透析治療において広く用いられてきた。

【０００３】当初これらの膜は、血液中の尿素、クレアチニンなどの低分子物質を除去することを主眼に開発、臨床供与されてきた。しかしながら、長期透析患者の増加に伴い、手根管症候群等の長期透析合併症が注目されるに至り、近年では、透析による除去対象物質は、尿素、クレアチニン等の低分子物質のみでなく、中分子量から高分子量の物質（低分子蛋白質）をも除去対象とすることがこれらの血液浄化膜に要求されている。これらの治療に用いられる膜は、ハイパフォーマンス膜（以下、ＨＰＭ）と呼ばれ、従来の透析膜より膜の孔径を拡大することにより、より大きな物質の除去を可能にしている。

【０００４】特に臨床上注目されている除去対象の高分子物質は、手根管症候群を引き起こすアミロイド化物質と考えられるβ2-ミクログロブリン（分子量１１６００ダルトン）であり、β2-ミクログロブリンの除去性に優れ、血液中の有用蛋白質であるアルブミン（分子量６６０００ダルトン）の分画をいかにシャープに行うかがＨＰＭの性能の善し悪しとなる。

【０００５】かかる問題に対しては、従来のセルロース膜は必ずしも最適な膜構造を与え得る素材とはいえず、このＨＰＭ分野では三酢酸セルロース、ポリアクリロニトリル、ポリスルホン等の合成系の素材が主体となっている。中でもポリスルホン系の透過膜は、中空繊維の成形加工性、製膜性に優れており、特開昭６１－９３８０１や特開平４－３００６３６には、親水性高分子をブレンドすることによりポリスルホン自体の疎水性による溶質透過性の低下を抑えた膜が開示されている。

【０００６】さらに近年、ＨＰＭの普及に伴い問題視されているのが、長期透析合併症に対するＨｅｎｄｅｒｓｏｎらの提示したインターロイキン仮説（Ｂｌｏｏｄ Ｐｕｒｉｆ．，１；３，１９８３）である。この考えによれば透析アミロイド症を引き起こす免疫的な遠程として、補体の活性化により単球が刺激され、そこに血中のエンドトキシンが作用し、単球からのインターロイキン（ＩＬ－１）が産生放出され、それが繊維芽細胞やコラーゲンの増産をおこし、また組織適合抗原クラス１の発現亢進により、β2-ミクログロブリン放出を引き起こし関節炎と骨へのアミロイド沈着の発症に至ることが示されている。長期透析患者では、透析膜と血液の接触による補体の活性化、および血液の体外循環施行（透析液等からのエンドトキシンの血液への侵入）等により慢性的なＩＬ－１産生刺激があり合併症に至る。

【０００７】かかる問題に対しては、三酢酸セルロース、ポリスルホン等は良好な生体適合性（低補体活性）の素材として知られている。しかしながらＨＰＭでは、膜孔径を拡大させているため外部からのエンドトキシンの侵入に対しては、逆に危険視される結果となってい

る。

【０００８】また、ＨＰＭでは、血液透析器の圧損と血液－透析液の浸透圧差の影響から血液浄化器の血液流入部では血液側が陽圧にも関わらず、血液出口付近では陰圧になってしまい透析液側からの逆濾過が生ずる’Ｂａｃｋｆｉｌｔｒａｔｉｏｎ’現象が起こることが知られており、この点からも血液へのエンドトキシン侵入の危険性が危惧されている。実際セルロース膜使用の患者群とＨＰＭ系の合成膜使用の患者群ではエンドトキシン抗体陽性率が後者の方が高いことが報告されている。（Ｔｒａｎｓ．Ａｍ．Ｓｏｃ．Ａｒｔｉｆ．Ｉｎｔｅｎ．Ｏｒｇａｎｓ，３５；３３１，１９８９）

【０００９】ここでエンドトキシンとは、グラム陰性菌の細胞壁由来のリポ多糖あるいはそのタンパク複合体であり、活性を有する最小のフラグメントはリピドＡであり分子量は数千である。従って、分画分子量数万のＨＰＭは、エンドトキシンは透過されることとなる。同様に前記の従来技術として開示されているポリスルホン中空糸膜もエンドトキシンの非透過性を保証できるものではない。これに対して、臨床使用時にエンドトキシンフリーの透析液を使用することが推奨されているが、装置、ランニングコストが嵩む不利益があり、またエンドトキシンフリーを完全に実施するには人の作業も含めた透析施設全体の徹底的なバリデーション無しには現在不可能である。

【００１０】また、透析液の供給ラインの血液浄化器直前にエンドトキシン除去フィルターを設けることも行われている。しかしエンドトキシンが血液浄化器への接続部に濃縮されているとの報告もあり、最終的には、血液浄化器自体がエンドトキシンを侵入させない機能を有することが理想といえる。

【００１１】これに対して前記の従来技術として開示されているポリスルホン膜は、そもそもエンドトキシンに対する記述は無く、さらに膜構造が、透析液側（中空糸の外表面）にサブミクロンからミクロンオーダーの開孔を有する非対称構造になっていることから、この大きな開孔部からのエンドトキシン侵入が危惧され、かつ内表面に厚さ数ミクロン見らず（３ミクロン以下）の分離層があるのみであり、この層に一部の欠陥を生じただけでエンドトキシンが血中に侵入する確率が高くなる。

【００１２】ポリスルホン系膜そのものにエンドトキシン吸着能を付与する技術としては、特開平７－１１６４８４に、カチオン性樹脂で膜を処理しイオン的な相互作用でエンドトキシンを吸着させる方法が開示されている。しかしながらエンドトキシンの全成分がアニオン的であるわけではなく、また透析液、血液といった高電解質濃度下での効果については疑問である。また、血液浄化膜として用いるにはカチオン樹脂コートによる膜性能低下、溶出物等の安全性の面から必ずしも適用できるものではない。

【００１３】また、エンドトキシンの選択吸着剤としては、ヒスチジン固定材（発酵工学会誌、６５巻、５号、４４６、１９８７）あるいはポリミキシン固定材（特開平５－３０５１３９）があるが、これらはエンドトキシン含有液を直接循流により吸着除去するための手法であり、本発明でいう血液浄化膜に適用される技術ではない。

【００１４】

【発明が解決しようとする課題】本発明の課題は、血液浄化時に、β2-ミクログロブリン等の有害な低分子蛋白質の除去性能に優れつつも、透析液側から血液側に実質的にエンドトキシンを逆濾させない、高い透析性能と安全性を兼ね備えた血液浄化膜を提供することにある。

【００１５】かかる課題を解決するために鋭意検討した結果、本願発明者らは、中空糸膜の膜全域の疎水性高分子と親水性高分子の構成ポリマー比を適切な範囲とし、中空糸膜全体に適度な親水性・疎水性を付与することにより、血液側から透析液側へ不要な低分子蛋白質を除去しつつも、透析液側から血液側へのエンドトキシンの汚染をなくすことが可能となることを見い出した。さらに、中空糸膜の膜構造をボイドや網目構造を含まない、実質的に均一な構造とすることにより、膜全体でエンドトキシンを阻止し得ることを見い出した。

【００１６】また、官能基として芳香族を有する高分子にはエンドトキシン吸着能があり、かような芳香族系の高分子により中空糸膜を構成することにより、さらにエンドトキシンによる汚染防止を容易に達成し得ることを見い出した。かような芳香族系の高分子にエンドトキシンが吸着するのは、エンドトキシンが、エンドトキシン結合蛋白やリピドＡの脂質部に由来して、ある程度疎水性面に吸着性を持つためと考えられる。

【００１７】さらに、前記のＨＰＭの必要特性である低分子タンパク領域（分子量２万弱）の透過性と高度なエンドトキシン除去を両立させるため、本発明者らは従来の血液浄化膜で成し得ていない透析液側（中空糸外側）の細孔制御技術を開発した。これにより均一膜構造の中空糸外面にも緻密層と細孔をもたせ、中空糸外面からのエンドトキシンの侵入の抑制と吸着、さらに溶質透過を行う細孔部に侵入したエンドトキシンに対しても膜厚部全体の広い吸着面積でエンドトキシンを吸着し得ることを見い出した。

【００１８】中空糸外面の細孔制御は、前記の相分離法による中空糸紡糸過程において、ノズルから吐出された紡糸原液が凝固浴にて、中空糸外面から脱溶媒される際に、同時に外表面近傍の親水性高分子はわずかに凝固浴中に脱落し、さらに水洗等の処理により、疎水性膜部への滞留の不安定なものは完全に落とされる。この親水性高分子の脱落部は、膜の外表面部にサブミクロン以下の微細な孔を形成し、この細孔による活性炭的効果によりエンドトキシンの吸着能を増加させることができると考

えられる。

【００１９】外表面の細孔の評価は、ＳＥＭ、原子間力顕微鏡、レプリカ法等によりある程度の観察の可能性はある。しかし、中空糸が膜構造保持剤で覆われている点、よしんば膜構造保持剤を除いた状態（凍結乾燥させたもの、あるいは濡れた状態でのクライオＳＥＭ、低真空ＳＥＭ）での観察が可能であっても現在の科学技術ではサブミクロン以下の正確な表面細孔評価は困難と思われる。また、ＢＥＴ法、水銀圧入法による細孔そのものの評価法はあるが、これらは表面のみといった局所的な部位の評価は不可能である。本発明者らは、間接的な評価として最外表面の親水性高分子の存在率を表面ＩＲ法で見ることを検討したが、精度の問題と数μｍ深度の情報が混在するため微量の差異評価は困難であった。以上の経緯により、本発明者らは、ＨＰＭとしての溶質透過性をもち、かつエンドトキシンに対する吸着性と侵入阻止の両立を実現させた血液浄化膜を開発するに至った。

【００２０】本発明は、上記の知見に基づきさらに検討を重ねて完成したものである。

【００２１】すなわち、本願発明は、中空糸膜を構成する全（疎水性及び親水性）高分子に対する親水性高分子の含有率が５～２０重量％、疎水性高分子の含有率が９５～８０重量％である中空糸膜であって、膜中空糸膜の内表面、外表面及び膜中間部における親水性高分子の含有率（内表面がＡ％、外表面がＢ％、膜中間部がＣ％）が下記の式を満たす中空糸膜を提供するものである。

（（Ａ－Ｘ）^{2}＋（Ｂ－Ｘ）^{2}＋（Ｃ－Ｘ）^{2}）０．５／Ｘ≦０．５

但し、Ｘ＝（Ａ＋Ｂ＋Ｃ）／３

【００２２】好適な実施態様においては、前記中空糸膜の膜断面を３００倍の電子顕微鏡で観察するとき、明らかに認められるボイドまたは網目構造が存在せず、前記中空糸膜の内部構造が実質的に均一構造である。

【００２３】好適な実施態様においては、前記中空糸膜の内表面及び外表面を５０００倍の電子顕微鏡で観察するとき、明らかに認められる孔が存在せず、前記中空糸膜の表面構造が実質的に平滑構造である。

【００２４】好適な実施態様においては、前記中空糸膜を充填した内表面積換算で１ｍ^{2}のモジュールにヘマトクリット３０％、蛋白質濃度７ｇ／ｍｌの牛血液を流速２００ｍｌ／分で流し、濾過流速１０ｍｌ／分で濾過を行った時の、牛血液中のβ２-ミクログロブリンの篩い係数が５０％以上である。

【００２５】好適な実施態様においては、前記疎水性高分子が芳香族ポリスルホン系高分子である。

【００２６】好適な実施態様においては、前記親水性高分子がポリビニルピロリドンである。

【００２７】好適な実施態様においては、前記中空糸膜が膜構造保持剤として多価アルコールを含む。

【００２８】以下、本願発明を詳細に説明する。

【００２９】本発明の中空糸膜に用いられる疎水性高分子は、セルロース系、ビニル系、芳香族系のいづれのものに限定されるものではないが、エンドトキシンに対する吸着性が比較的高い芳香族系の高分子、例えば、芳香族ポリスルホン系高分子、芳香族ポリアミド系高分子、芳香族ポリイミド系高分子、芳香族ポリエーテル系高分子、芳香族ポリエステル系高分子、芳香族ポリケトン系高分子、芳香族ポリサルフェート系高分子等が好ましい。さらに中空糸加工性、製膜性、生体適合性の観点から芳香族ポリスルホン系高分子が特に好ましい。なお、上記の芳香族ポリスルホン系高分子とは、分子中に芳香族官能基を有するポリスルホン系高分子であれば特に限定されるものではなく、例えば、芳香族ポリスルホン、芳香族ポリエーテルスルホン等が挙げられる。

【００３０】本発明の中空糸膜に用いられる親水性高分子は、ポリビニルアルコール、ポリエチレングリコール、ポリプロピレングリコール、ポリビニルピロリドン、ポリエチレンイミンおよびそれらの共重合体等からなる合成高分子、あるいは多糖類が挙げられる。さらにこの中でも上記疎水性高分子との相溶性、製膜性等の観点からポリビニルピロリドンが特に好ましい。

【００３１】本発明の中空糸膜を構成する全（疎水性及び親水性）高分子中の親水性高分子の含有率は５～２０重量％、疎水性高分子の含有率は９５～８０重量％である。親水性高分子の含有率が５重量％未満である場合には、エンドトキシン吸着性はあるものの本発明の目的とするＨＰＭとしての十分な溶質透過性が得られない。親水性高分子の含有率が２０重量％を越える場合には、親水性高分子の溶出する可能性が高くなり安全面から問題になる。好ましい親水性高分子の含有率は８～２０重量％であり、特に好ましい含有率は１２～１６重量％である。

【００３２】なお、膜全体の親水性高分子の含有率は、膜構造保持剤を適当な処理（水洗、乾燥等）により除き膜を構成する高分子材のみにさせた後、中空糸を粉砕し均一化し、または適当な溶媒に均一溶解させ、元素分析、分子振動分析、ＮＭＲ等の手法により親水性高分子の含有率を測定することができる。元素分析で行う場合は、親水性高分子または疎水性高分子にのみ存在する元素の含有率を求め、分子構造からいずれかの高分子全体の含有率を求める。分子振動分析（例えばＩＲ分析）、ＮＭＲでは、親水性高分子または疎水性高分子に特有の吸収バンド、ケミカルシフト等の強度から含有率を求めることができる。前記の何れの方法によっても親水性高分子の含有率は求め得るが、本発明においては、膜全体の親水性高分子の含有率をＩＲ分析により測定した。測定法の詳細は膜全体の親水性高分子の含有率の測定の欄に記載の通りである。

【００３３】また、本発明の中空糸膜は、膜の内表面、外表面及び膜中間部における親水性高分子の含有率（内

表面がA%、外表面がB%、膜中間部がC%）が下記の式を満たす。

（（A－X）^{2}＋（B－X）^{2}＋（C－X）^{2}）０．５／X≦０．５

但し、X＝（A＋B＋C）／３

この式の値が０．５を越える場合には、親水性高分子又は疎水性高分子に偏った高分子組成となり、エンドトキシンの吸着性が低下する。また、この式の値が０．５以下であることは、膜全体が適度な緻密性を有し、エンドトキシンを膜全体で阻止し得ることとなる。好ましい式の値は、０．４以下である。なお、この式は膜の各部位（内表面、外表面、中間部）の親水性高分子の分布状態を示し、この式の値が小さいほど各部位に親水性高分子が均一に分布し、その含有率も一定であることを示し、この式の値が大きいほど各部位の親水性高分子の分布が不均一で、各部位の親水性高分子の含有率に大きな差があることを示す。以後、この式の値を親水高分子分布比とする。

【００３４】なお、膜の各部位の親水性高分子の含有率は、表面分析手法に基づき各種エネルギー、分子振動分析から評価することができる。本発明では、顕微ＦＴ－ＩＲ分析により膜の、内表面、中間部、外表面に含有される親水性高分子と疎水性高分子に由来するバンド強度の比から各部位での親水性高分子の含有率を測定する。測定法の詳細は膜の各部位の親水性高分子の含有率の測定の欄に記載の通りである。

【００３５】本発明の中空糸膜は、膜の断面を３００倍の電子顕微鏡で観察するとき、明らかに認められるボイドまたは、網目構造が存在しない。上記で、膜の断面を３００倍の電子顕微鏡で観察するとき、明らかに認められるボイドまたは、網目構造が存在しないとは、膜内部構造が実質的に空洞を伴たない均一構造であることを意味し、かように本発明の中空糸膜は均一構造であることにより、透析液側から血液側へのエンドトキシンの移動を膜全体で阻止することが可能となる。

【００３６】本発明の中空糸膜は、膜の内表面及び外表面を５０００倍の電子顕微鏡で観察するとき、明らかに認められる孔が存在しない。膜の内表面及び外表面を５０００倍の電子顕微鏡で観察するとき、明らかに認められる孔が存在しないとは、膜の表面構造が実質的に平滑構造であることを意味し、かように本発明の中空糸膜は平滑構造であることにより、実際に血液を処理する場合にも、孔の目詰まりが少なく、分画２次層も薄く形成されることとなり、β2-ミクログロブリン等の不要な低分子蛋白質の高い除去性能を維持することが可能となる。

【００３７】なお、一般的に、膜構造は走査型電子顕微鏡（ＳＥＭ）による評価が常套手段であり、本願においても電子顕微鏡による観察に基づき膜構造を評価した。なお、本発明の膜構造は前記で説明した通り、実質的に均一且つ平滑な構造である。かような均一性及び平滑性を評価するためには、本来できるだけ大きな倍率の電子顕微鏡で観察し評価すべきであるが、電子顕微鏡が発生する熱による膜構造への影響を回避するためには、現状では５０００倍が上限である。よって、本願においては、膜の平滑性の評価を５０００倍の電子顕微鏡により中空糸膜の内表面及び外表面を観察することにより評価した。ここで、孔が存在しないとは、５０００倍の拡大写真での観察限度が０．２mmとした場合、４００オングストローム以上の孔や空洞が存在しないことを意味する。

【００３８】本発明の中空糸膜は、膜厚が数μm～８０μmであり、外径が１００μm～５００μmの真円形の横断面を有するのが好ましい。前記したように本発明の中空糸膜は実質的に均一構造であるから、溶質の分離効率を向上させるには膜厚を下げることが望まれ、好ましくは膜厚が１５μm～４０μmであり、外径が２００～３００μmである。

【００３９】本発明の中空糸膜を充填した内表面積換算で１m^{2}のモジュールにヘマトクリット３０%、蛋白質濃度７g／m１の牛血液を濾速２００m１／分で流し、濾過流速１０m１／分で濾過を行った時の、牛血液中のβ2-ミクログロブリンの篩い係数は５０%以上である。篩い係数が５０%以下では、β2-ミクログロブリンの除去率が不十分である。また、本発明においては、β2-ミクログロブリンの除去率を上記のように実際に血液を流した場合の除去率で規定した。これは、中空糸膜に実際に血液を流した場合、前記のように分極２次層が形成され、水系での篩い係数と血液系での篩い係数では大きな差を生じるためである。

【００４０】また、ここでいう５０%以上の透過性とは、中空糸に供給される液と通過した液および膜を透過した液、各々に含まれるβ2-ミクログロブリン濃度を用いて下記式で示される篩い係数（ＳＣ）で定義される。

ＳＣ（%）＝（Ｔ１×２）／（Ｔ２＋Ｔ３）×１００

但し、Ｔ１：透過液中のβ2-ミクログロブリン濃度

Ｔ２：供給液中のβ2-ミクログロブリン濃度

Ｔ３：通過液中のβ2-ミクログロブリン濃度

【００４１】本発明の中空糸膜は、膜構造が膜構造保持剤により保持されているのが好ましい。膜構造保持剤は血液浄化器として用いられる際に容易に水、生理食塩水等で洗浄、除去される物質である必要があり、水溶性の物質であることが好ましい。例えば、グリセロール、グリコール等の多価アルコール、多糖類、または界面活性剤等が挙げられる。中でも、グリセリンは血液浄化膜としての安全性、およびポリスルホン系均一膜の緻孔内部への導入が容易であり特に好ましい。

【００４２】本発明の中空糸型血液浄化膜を作成する方法としては、例えば、疎水性高分子と親水性高分子を溶媒、あるいは、溶媒と貧溶媒の混合液からなる溶剤に溶解してドープ原液を調製し、これをノズルから吐出させ

凝固液中で相分離による膜形成を行わせる方法が挙げられる。この方法では、膜の細孔の孔径分布を狭くし、シャープな血液成分の分画特性を得ることが可能となる。また、適当なドープ条件、凝固条件を選ぶことによって様々な溶質分離特性を膜に与えることが可能である。

【００４３】また中空部の形成には、中空部形成芯剤を用いることが必要であり、この芯剤は同時に凝固液として用いる場合がある。従来のポリスルホン系の膜ではこの手法により製膜されており内面が密に凝固した非対称膜が形成される。それに対して芯剤にガス、あるいは、低凝固性の流体を用いることにより均一膜を得ることができる。さらに非対称構造の場合、親水高分子が緻密層に局在しやすいのに対し、芯剤にガス等を用いた場合には、比較的均一に膜全体に親水高分子を導入することができ、膜全体で親水性、疎水性のバランスの良好な構造を有する膜を得ることが可能となる。

【００４４】さらに形成された中空糸膜は、水洗、乾燥等の処理を行う。この乾燥工程で支持層を持たない均一膜は、乾燥に伴う水の表面張力等により膜が収縮し、相分離法で調製された膜性能を低下することが多い。これを防ぐためには、膜構造保持剤を膜構造中に含ませることが好ましい。膜構造保持剤は水洗後、乾燥工程の前に導入されるのが最も最適である。

【００４５】本発明の中空糸型血液浄化膜は、具体的には例えば以下のように製造することができる。

【００４６】疎水性高分子１５から３５重量%、親水性高分子２～５重量%、溶媒３０～６０重量%、非溶媒１０～５０重量%を含む紡糸原液を５０～１９０℃に加熱して溶解させ、二重管ノズルの外側から押し出し、中央からは気体もしくは紡糸原液に対し凝固性が無いか、あるいは凝固性の低い液体を送り込む。押し出された紡糸原液は、１～２０mmの空中を走行させた後、５～６０℃の凝固性液体を通って凝固され水洗された後、４０～６０重量%のグリセリン水溶液中を通過し、グリセリンを含浸させた後、乾燥機にて乾燥させる。

【００４７】上記の溶媒としては、Ｎ，Ｎ－ジメチルホルムアミド、Ｎ，Ｎ－ジメチルアセトアミド、Ｎ－メチルピロリドン、γ－ブチロラクトンなどの極性溶媒を単独もしくは混合で用いることができる。上記の非溶媒としては、エチレングリコール、トリエチレングリコール、ポリエチレングリコール、プロパンジオール、ブタンジオールなどのポリオール類、あるいはエチレングリコールモノエチルエーテル、ジエチレングリコールモノエチルエーテルなどのエーテル類を単独もしくは混合して使用することができる。また、中空形成剤としては、窒素、アルゴン、酸素、炭酸ガス、ヘリウム、空気等のガスあるいは流動パラフィン、ミリスチン酸イソプロピル、植物、鉱物油等の油脂類、あるいはその他の低凝固性液体を使用することができる。本発明で用いることのできる溶媒、非溶媒、中空形成剤は上記に限られるものではない。

【００４８】以下、実施例により本発明の内容をさらに詳細に説明するが、本発明は以下により何等限定されるものではない。

【００４９】まず、本発明の血液浄化膜のβ２-ミクログロブリン、エンドトキシン、溶出物、親水性高分子含量の測定方法について説明する。

【００５０】１．β２-ミクログロブリンのＳＣ（%）試験

血液浄化膜１００００本程度の中空糸をプラスチック成形品の中に入れ両端が開口した内表面換算で、膜面積約１m^2のモジュールを作製する。このモジュールを生理食塩水による洗浄後、血液側（中空糸内側）に、抗凝固処理したヘマトクリット３０%の牛新鮮血を２００ｍｌ／分で流す。モジュールの内表面換算で、膜面積１m^2当たりの濾過速度１０ｍｌ／分となるように透析液側に接続したポンプにより血液濾過を行い下記について測定、前記のＳＣ（%）を計算する。血液濾過開始１５分時点のモジュールの入口、出口の血液、および濾過液をサンプリングして、酵素免疫測定法（たとえば、β２-ＭＧ-ＥＩＡ　ＴＥＳＴ　和光純薬工業）等によりβ２-ミクログロブリンの濃度を測定する。なお、当該測定で用いる牛血液にはあらかじめヒト由来のβ２-ミクログロブリンを添加して行う。これらのβ２-ミクログロブリンの濃度から式１に従ってＳＣ（%）を求める。

【００５１】２．エンドトキシン吸着試験

測定用中空糸膜の外表面換算で、膜面積０．０５m^2の中空糸膜を１ｃｍの長さに刻みガラス容器に入れ、エンドトキシンフリー水を５０ｍｌ添加し、浸漬－デカンテーションを３回繰り返し最後にエンドトキシン溶液（約７．０ＥＵ／ｍｌ）３０ｍｌを加え、３７℃にて１時間インキュベートし、その後液をサンプリングして、エンドトキシンを定量する。エンドトキシンの測定には、比色定量法（生化学工業製トキシカラーシステム）で行う。（検出限界は０．２ＥＵ／ｍｌ）なお、本実験で使用するガラス器具、鉄等は全てあらかじめ２６０℃乾熱滅菌を施したものを使用し、測定はクリーンベンチで実施する。

【００５２】また、モジュールでのエンドトキシン除去は、以下の方法により測定する。

【００５３】３．エンドトキシン透過試験

評価サンプルは、上記ＳＣ（%）評価と同様の透析器を使用し、まずモジュールおよび接続回路全体を超純水（ミリポア社製、ｍｉｌｌｉ－Ｑシステム）を用いて十分にシングルパスで洗浄する。ついで透析器の血液側（中空糸内側）を流れる液を循環系にし２００ｍｌ／分で流す（循環水の総量２１）。この時点で循環液をサンプリングし初期のエンドトキシン濃度を求める。また同時に透析側にエンドトキシン含有液（市水とＲＯ水の混合水；約２．０ＥＵ／ｍｌ）を５００ｍｌ／分で向流で

シングルパスで流し、ＵＦＲコントローラー付きの透析装置（ニプロ社製、ＮＣＵ－６）を用い膜間の透水量をほぼ０にする。２時間経過後血液側の循環水をサンプリングする。サンプリング液は、前記の手法で同様にエンドトキシン濃度を測定する。エンドトキシンの透過試験測定のダイナミックレンジは、０．０２～０．１５ＥＵ／ｍｌで実施した。また、初期のエンドトキシン濃度は検出限界以下であった。

【００５４】４．溶出物試験

人工腎臓承認基準試験（日本人工臓器工業協会）に基づき、抽出液の紫外吸収スペクトル（ＵＶ）により測定する。合格基準は、ＵＶが０．１以下である。

【００５５】５．膜全体の親水性高分子の含有率の測定

親水性高分子と疎水性高分子との含有率は、本発明では紡糸原液の仕込み比率と殆ど同じか若干の低下となるが、中空糸形成後の存在比の確認は、以下の方法で行った。中空糸を、適当な溶媒に均一に溶解後、ＫＢｒ錠剤に塗布、乾燥させ透過ＩＲを測定する。これによりＩＲバンドの親水性高分子由来、疎水性高分子由来のピーク強度比を見積もる。親水性高分子と疎水性高分子の配合比（重量％）が既知のサンプルで同様に測定し、検量線を作成し、これにより中空糸中の親水性高分子の含有率（全高分子に対する親水性高分子の重量％）を計算する。

【００５６】６．膜の各部位の親水性高分子の含有率の測定

親水性高分子の分析評価は、中空糸を縦に切り、広げた試料について、内側、外側の表面ＩＲを測定する。中間部は、表層を削り取り中間部を露出した試料について同様に測定する。中間部は、ほぼ膜厚部の中央部分とした。表面ＩＲはＦＴ－ＩＲ顕微ＡＴＲ法（ＩＥＲ；ダイアモンド）により行った。この条件では試料表面の約１．５μｍの層を測定している。同様にピーク強度を比較し強度比を求めた。但しこの場合は、検量線作成による含有率の見積もりは困難なため、ピーク強度比そのものの比から膜の内表面、外表面、中間部での親水性高分子の含有率を見積もった。すなはち、この強度比は、各部位の親水性高分子、疎水性高分子の規格化された含有率を表すので、この値を用いて膜の親水性高分子分布比を算出した。

【００５７】（実施例１）ポリエーテルスルホンが２２重量％、ポリビニルピロリドン（Ｋ－９０）３．０重量％、溶媒としてＮ－メチルー２－ピロリドンが３７．５重量％、非溶媒としてポリエチレングリコール＃２００が３７．５重量％からなる原料を１２０℃に加熱溶解した溶液を、二重管ノズルの外側から押し出し、中心からは、窒素を送り込んで中空糸状とし、水、Ｎ－メチルー２－ピロリドン、ポリエチレングリコール＃２００が６０：２０：２０の重量比で混合して成る、温度４０℃の凝固性液体中を通過させ、凝固させた。その後、水洗し、５０重量％のグリセリンを含浸させたのち乾燥機にて乾燥させ、内径２０１μｍ、膜厚２８μｍの中空糸膜を得た。得られた中空糸の断面の３００倍ＳＥＭ像からは、ボイド、または網目構造は観察されず、内外表面の５０００倍ＳＥＭ像からは孔は確認されなかった。ＩＲ分析からの親水性高分子の含有率は約１２％であった。内面、中層、外面の親水高分子の強度比は、外面＞中層＞内面であり、分布比は０．２１であった。これは図１、図２、図３に表面ＩＲの測定例をしめすが、１６７０ｃｍ－１のポリビニルピロリドンのカルボニル吸収、１５７０ｃｍ－１のポリエーテルスルホンの芳香族の吸収の強度比（Ａ1670／Ａ1570）から計算した。以下の実施例及び比較例においても同様に測定した。この中空糸のβ2-ミクログロブリンのＳＣ（％）は７３％であり、エンドトキシン吸着試験では、浸漬後の液のエンドトキシン濃度は検出限界以下、モジュールでのエンドトキシン透過試験でも血液側のエンドトキシン濃度は検出限界以下であり、エンドトキシンの血液側への侵入は殆ど無かった。また溶出物試験は、ＵＶ＝０．０４と合格した。

【００５８】（実施例２）ポリエーテルスルホンが２１重量％、ポリビニルピロリドン（Ｋ－９０）３．５重量％、溶媒としてＮ－メチルー２－ピロリドンが３７．７５重量％、非溶媒としてトリエチレングリコールが３７．７５重量％からなる原料を１２０℃に加熱溶解した溶液を、二重管ノズルの外側から押し出し、中心からは、窒素を送り込んで中空糸状とし、水、Ｎ－メチルー２－ピロリドン、トリエチレングリコールが６０：２０：２０の重量比で混合して成る、温度４０℃の凝固性液体中を通過させ、凝固させた。その後、水洗し、５０重量％のグリセリンを含浸させたのち乾燥機にて乾燥させ、内径２０２μｍ、膜厚３２μｍの中空糸膜を得た。得られた中空糸の断面の３００倍ＳＥＭ像からは、ボイド、または網目構造は観察されず、内外表面の５０００倍ＳＥＭ像からは孔は確認されなかった。ＩＲ分析からの親水性高分子の含有率は約１４％であった。内面、中層、外面の親水高分子の強度比は、外面＞中層＞内面であり、分布比は０．１１であった。この中空糸のβ2-ミクログロブリンのＳＣ（％）は７５％であった。エンドトキシン吸着試験では、浸漬後の液のエンドトキシン濃度は０．５ＥＵ／ｍｌであり吸着が見られた。モジュールでのエンドトキシン除去試験でも血液側のエンドトキシン濃度は検出限界以下であり、エンドトキシンの血液側への侵入は殆ど無かった。また溶出物試験は、ＵＶ＝０．０８と合格した。

【００５９】（比較例１）ポリエーテルスルホンが２７重量％、ポリビニルピロリドン（Ｋ－９０）１．０重量％、溶媒としてＮ－メチルー２－ピロリドンが３６．０重量％、非溶媒としてポリエチレングリコール＃２００が３６．０重量％からなる原料を１２０℃に加熱溶解し

た溶液を、二重管ノズルの外側から押し出し、中心からは、窒素を送り込んで中空糸状とし、水、Ｎ－メチル－２－ピロリドン、ポリエチレングリコール＃２００が６０：２０：２０の重量比で混合して成る、温度４０℃の凝固性液体中を通過させ、凝固させた。その後、水洗し、５０重量％のグリセリンを含浸させたのち乾燥機にて乾燥させ、内径２０１μｍ、膜厚２８μｍの中空糸膜を得た。得られた中空糸の断面の３００倍ＳＥＭ像からは、ボイド、または網目構造は観察されず、内外表面の５０００倍ＳＥＭ像からは孔は確認されなかった。ＩＲ分析からの親水高分子の含有率は約３．５％であった。内面、中層、外面の親水高分子の強度比は、外面＞中層＝内面であり、分布比は０．１４であった。この中空糸のβ2-ミクログロブリンのＳＣ（％）は２５％であり、ＨＰＭ要件を満たさなかった。エンドトキシン吸着試験では、浸漬後の液のエンドトキシン濃度は０．２ＥＵ／ｍｌ以下であり吸着がみられた。モジュールでのエンドトキシン除去試験でも血液側のエンドトキシン濃度は検出限界以下であり、エンドトキシンの血液側への侵入は殆ど無かった。また溶出物試験は、ＵＶ＝０．０２と合格した。

【００６０】（比較例２）ポリエーテルスルホンが２５重量％、ポリビニルピロリドン（Ｋ－９０）５．０重量％、溶媒としてＮ－メチルー２－ピロリドンが３５．０重量％、非溶媒としてポリエチレングリコール＃２００が３５．０重量％からなる原料を１２０℃に加熱溶解した溶液を、二重管ノズルの外側から押し出し、中心からは、水、Ｎ－メチル－２－ピロリドン、ポリエチレングリコール＃２００が６０：２０：２０の重量比で混合して成る凝固性の液体を流して中空糸状とし、水、Ｎ－メチル－２－ピロリドン、ポリエチレングリコール＃２００が６０：２０：２０の重量比で混合して成る、温度４０℃の凝固性液体中を通過させ、凝固させた。その後、水洗し、５０重量％のグリセリンを含浸させたのち乾燥機にて乾燥させ、内径２０１μｍ、膜厚４０μｍの中空糸膜を得た。得られた中空糸の断面の３００倍ＳＥＭ像からは網目構造が観察され、外表面の５０００倍ＳＥＭ像からは孔が確認され均一膜ではなく、非対称膜であった。ＩＲ分析からの親水高分子の含有率は５．０％であった。内面、中層、外面の親水高分子の強度比は、外面＜中層＜内面であり、分布比は０．７４であった。この中空糸のβ2-ミクログロブリンのＳＣ（％）は４５％であり、ＨＰＭ要件を満たさなかった。エンドトキシン吸着試験では、浸漬後の液のエンドトキシン濃度は２．５ＥＵ／ｍｌであり吸着がみられた。モジュールでのエンドトキシン除去試験では血液側のエンドトキシン濃度は０．１５ＥＵ／ｍｌ以上であり、エンドトキシンの血液側への侵入がみられた。また溶出物試験は、ＵＶ＝０．１１と不合格であった。

【００６１】

【表１】

	実施例１	実施例２	比較例１	比較例２
高分子の素材	ＰＥＳ ＰＶＰ	ＰＥＳ ＰＶＰ	ＰＥＳ ＰＶＰ	ＰＥＳ ＰＶＰ
膜構造保持剤	ｸﾞﾘｾﾘﾝ	ｸﾞﾘｾﾘﾝ	ｸﾞﾘｾﾘﾝ	ｸﾞﾘｾﾘﾝ
内径（μｍ）	２０１	２０２	２０１	２０１
膜厚（μｍ）	２８	３２	２８	４０
親水性高分子含有率 膜全体	１２％	１４％	３．５％	５％
親水性高分子分布比	０．２１	０．１１	０．１４	０．７４
変性化　内表面 含有率　外表面 (ﾋﾞｰﾀ強度比)中間部	０．３５ ０．４７ ０．４４	０．４８ ０．５６ ０．５３	０．１１ ０．１３ ０．１１	０．２３ ０．０８ ０．１３
膜断面構造	均一	均一	均一	非均一
膜内表面構造	平滑	平滑	平滑	平滑
膜外表面構造	平滑	平滑	平滑	多孔質
β2-MG篩い係数	７３％	７５％	２５％	４５％
ＥＴ試験(EU/ml)	ＮＤ	ＮＤ	ＮＤ	≧0.15
溶出物試験	０．０４	０．０８	０．０２	０．１１

（注）ＰＥＳ：ポリエーテルスルホン
ＰＶＰ：ポリビニルピロリドン
ＮＤ：検出限度以下(Not detect)

【００６２】

【発明の効果】以上の説明から明らかなように、本発明の中空糸膜は、実際に血液を流す系においてβ2-ミクログロブリンを５０%以上除去することが可能な高い透過性能を有し、且つ、血液側へのエンドトキシンの汚染を阻止し、エンドトシンに対する高い吸着性と阻止性を有する。かように、本発明の中空糸膜は、血液透析等の医療分野、特にＨＰＭ等において、より高い不要物質の除去性能を有し、且つ、より高い安全性を有するものであり、本願発明の中空糸膜により、高度な品質の治療を可能とするものである。以上の通り、本発明の中空糸膜の効果は大であり、今後、透析合併症への改善を新たな指標から開拓する血液透析等の分野において、大いにその利用が期待される。

【図面の簡単な説明】

【図１】本願実施例１の中空糸膜の内表面のＩＲスペクトルである。

【図２】本願実施例１の中空糸膜の外表面のＩＲスペクトルである。

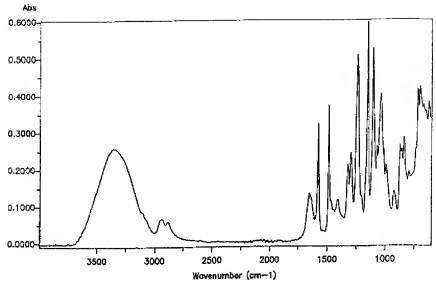
【図３】本願実施例１の中空糸膜の断面のＩＲスペクトルである

【図４】本願実施例１の中空糸膜の内表面の５０００倍の電子顕微鏡写真である。

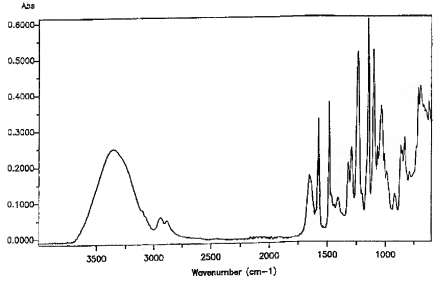
【図５】本願実施例１の中空糸膜の外表面の５０００倍の電子顕微鏡写真である。

【図６】本願実施例１の中空糸膜の断面の３００倍の電子顕微鏡写真である。

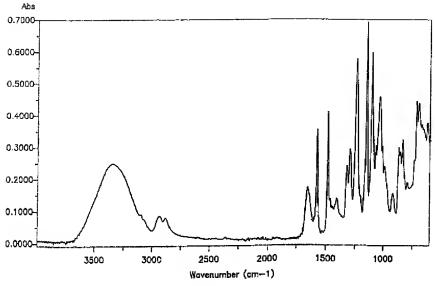
【図１】


Abs
0.6000
0.5000
0.4000
0.3000
0.2000
0.1000
0.0000
3500
3000
2500
2000
1500
1000
Wavenumber (cm-1)

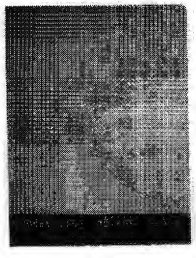
【図２】


Abs
0.6000
0.5000
0.4000
0.3000
0.2000
0.1000
0.0000
3500
3000
2500
2000
1500
1000
Wavenumber (cm-1)

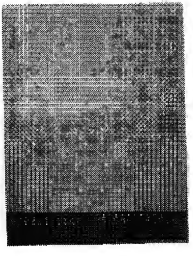
【図３】


Abs
0.7000
0.6000
0.5000
0.4000
0.3000
0.2000
0.1000
0.0000
3500
3000
2500
2000
1500
1000
Wavenumber (cm-1)

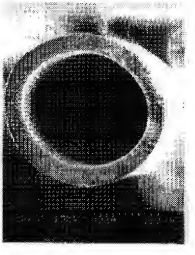
【図４】



【図５】



【図６】



I. PATENT ABSTRACTS OF JAPAN

(11)Publication number : **10-180058**
(43)Date of publication of application : **07.07.1998**

(51)Int.Cl. **B01D 69/08**
B01D 71/44
B01D 71/68
D01F 1/08
D01F 8/10

(21)Application number : **08-343858**
(22)Date of filing : **24.12.1996**

(71)Applicant : **TOYOBO CO LTD**
(72)Inventor : **KATO NORIAKI**
SHIODA YASUHIRO
YAMAMOTO ISAMU

(54) HOLLOW FIBER MEMBRANE

(57)Abstract:
PROBLEM TO BE SOLVED: To obtain a blood purifying membrane not passing endotoxin from the dialytic liq. side to the blood side by specifying the amts. of hydrophilic and hydrophobic polymers in a membrane and specifying the hydrophilic polymer content of the inner surface, outer surface and middle part of the membrane.
SOLUTION: This hollow fiber membrane consists of polymers including 5-20wt.% hydrophilic polymer and 95-80wt.% hydrophobic polymer. When the hydrophilic polymer contents of the inner surface, outer surface and middle part of this membrane are represented by A (%), B (%) and C (%), respectively, the relation of $[(A-X)2+(B-X)2+(C-X)2]0.5/X \leq 0.5$ [where $X=(A+B+C)/3$] is satisfied and the passing of endotoxin is prevented all over the membrane. In the case of $[(A-X)2+(B-X)2+(C-X)2]0.5/X>0.5$, the desired distribution of the polymers is not obtd. and endotoxin adsorbing property deteriorates.

LEGAL STATUS
[Date of request for examination] 03.08.1998
[Date of sending the examiner's decision of rejection]
[Kind of final disposal of application other than the examiner's decision of rejection or application converted registration]
[Date of final disposal for application]
[Patent number] 3314861

[Date of registration]	07.06.2002
[Number of appeal against examiner's decision of rejection]	
[Date of requesting appeal against examiner's decision of rejection]	
[Date of extinction of right]	

CLAIMS

[Claim(s)]
[Claim 1] The hollow fiber to which content of the hydrophilic macromolecule to the ** (hydrophobicity and hydrophilic property) macromolecule which constitutes a hollow fiber is characterized by for the content of a hydrophobic macromolecule being the hollow fiber which is 95 - 80 % of the weight, and filling the formula of the following [content / (for A % and an outside surface, B % and film pars intermedia are / an internal surface / C %) / of the hydrophilic macromolecule in the internal surface, outside surface, and film pars intermedia of this hollow fiber] five to 20% of the weight.
(A-X) 0.5 / X<=0.5, however X= (A+B+C)/3 -- [Claim 2] (2+(B-X) 2+(C-X) 2) The hollow fiber according to claim 1 which the void or the network structure accepted clearly does not exist, but is characterized by the internal structure of said hollow fiber being homogeneity structure substantially when observing the film cross section of said hollow fiber with a 300 times as many electron microscope as this.
[Claim 3] The hollow fiber according to claim 1 or 2 which the hole accepted clearly does not exist but is characterized by the surface structure of said hollow fiber being smooth structure substantially when observing the internal surface and outside surface of said hollow fiber with a 5000 times as many electron microscope as this.
[Claim 4] The film surface product of the internal-surface conversion filled up with said hollow fiber is 2 1m. Hollow fiber according to claim 1 to 3 characterized by the sieve multiplier of the beta 2-microglobulin in bovine blood liquid when filtering bovine blood liquid with a protein concentration of 7g [/ml] by part for 200ml/of the rates of flow hematocrit 30% to a module by part for sink and 10ml/of the filtration rates of flow being 50% or more.
[Claim 5] The hollow fiber according to claim 1 to 4 characterized by said hydrophobic macromolecule being an aromatic series polysulfone system macromolecule.
[Claim 6] The hollow fiber according to claim 1 to 5 characterized by said hydrophilic giant molecule being a polyvinyl pyrrolidone.
[Claim 7] The application-for-patent term 1 characterized by said hollow fiber containing polyhydric alcohol as a film structure-preserving agent thru/or a hollow fiber given in 6.

DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Field of the Invention] This invention relates to the hollow fiber used for blood purification etc.

as an artificial organ. Also when endotoxin is contained in a dialysing fluid side in blood purification etc. in more detail, maintaining the high removal engine performance of low-molecular protein, such as beta 2-microglobulin, it is related with the hollow fiber which does not make the endotoxin invade into a blood side substantially.

[0002]

[Description of the Prior Art] From the former, the permeable membrane and ultrafiltration membrane using a polymer, such as a cellulose, cellulose acetate, polymethylmethacrylate, and a polyacrylonitrile, are used in the medical field for the purpose which removes the wastes in blood. The cellulose wall has been especially used widely in the dialysis treatment for the prolongation of life and social rehabilitation of a renal failure patient.

[0003] For the purpose of removing low-molecular matter, such as a urea in blood, and a creatinine, it has been developed and clinical supply of these film has been carried out at the beginning. However, it is required for these blood purification film that the quality of a removal object by dialysis should make not only low-molecular matter, such as a urea and a creatinine, but the matter (low-molecular protein) of inside molecular weight to the amount of macromolecules applicable to removal in recent years with the increment in a long-term dialysis patient by long-term dialysis complication, such as a carpal tunnel syndrome, coming to attract attention. The film used for these therapies is called the high performance film (following, HPM), and enables removal of the bigger matter by expanding a membranous aperture from the conventional permeable membrane.

[0004] It becomes right and wrong of the engine performance of HPM how fractionation of the albumin (molecular weight of 66000dalton) which is the useful protein in blood is performed to Sharp by the high polymer for [which attracts attention especially on clinical] removal being beta 2-microglobulin (molecular weight of 11600dalton) considered to be the quality of an amyloid ghost which causes a carpal tunnel syndrome, and excelling in the removal nature of beta 2-microglobulin.

[0005] To this problem, the conventional cellulose wall cannot necessarily say it as the material which can give the optimal membrane structure, but the material of synthetic systems, such as a cellulose triacetate, a polyacrylonitrile, and polysulfone, serves as a subject in this HPM field. Especially, the transparency film of a polysulfone system is excellent in the fabrication nature of a hollow fiber, and film production nature, and the film which suppressed the fall of solute permeability by the hydrophobicity of the polysulfone itself is indicated by JP,61-93801,A and JP,4-300636,A by blending a hydrophilic giant molecule.

[0006] Furthermore, the interleukin assumption (3 Blood Purif., 1; 1983) which Henderson and others to long-term dialysis complication presented is regarded as questionable with the spread of HPM(s) in recent years. according to this idea, as an immunity-process which causes the dialysis amyloidosis, monocyte is stimulated by activation of complement, the endotoxin in blood acts there, and the interleukin (IL-1) from monocyte carries out production emission -- having -- it -- growth of fibrocyte or a collagen -- starting -- moreover, manifestation sthenia of the human leucocyte antigen class 1 -- beta 2-microglobulin emission -- causing -- the amyloid to arthritis and a bone -- resulting in the self-possessed onset is shown. In a long-term dialysis patient, there is a chronic IL-1 production stimulus by activation of permeable membrane and the complement by contact of blood, extracorporeal circulation enforcement (invasion into the blood of the endotoxin from dialysing fluid etc.) of blood, etc., and it results in complication.

[0007] To this problem, a cellulose triacetate, polysulfone, etc. are known as a material of good biocompatibility (low complement activity). However, in HPM, since the film aperture is made

to expand, to invasion of the endotoxin from the outside, a result by which dangerous ** is carried out conversely has been brought.
[0008] Moreover, in HPM, in the blood inflow section of blood purifier, a blood side becomes negative pressure from the effect of the pressure loss of the hemodialyzer, and the osmotic pressure difference of blood-dialysing fluid near a blood outlet in spite of positive pressure, it is known that the 'Backfiltration' phenomenon which the reverse filtration from a dialysing fluid side produces will happen, and it is apprehensive about the danger of endotoxin invasion into blood also from this point. It is actually reported by the patient group of cellulose wall use, and the patient group of synthetic membrane use of a HPM system that latter one has a high rate of endotoxin antibody-positive. (Trans.Am.Soc.Artif.Inten.Organs,35;331,1989)
[0009] Endotoxin is the lipopolysaccharide or its protein complex of the cell wall origin of a gram negative, the minimum fragmentation which has activity is lipid A, and molecular weight is thousands here. Therefore, endotoxin will be penetrated for HPM with 10,000 cuts off molecular weight. The polysulfone hollow fiber currently similarly indicated as the aforementioned conventional technique cannot guarantee the nontransparent nature of endotoxin, either. on the other hand, the time of clinical use -- endotoxin -- although using free dialysing fluid is recommended, current is impossible without the thorough validation of the whole dialysis facility which there is disadvantageous profit to which equipment and a running cost increase, and also included people's activity in carrying out an endotoxin free-lancer completely.
[0010] Moreover, preparing an endotoxin removal filter just before the blood purifier of the supply line of dialysing fluid is also performed. However, there is also a report that endotoxin is condensed by the connection to blood purifier, and having the function in which the blood purifier itself does not make endotoxin invade, finally can call it an ideal.
[0011] On the other hand, the polysulfone film currently indicated as the aforementioned conventional technique first of all, from there being no description to endotoxin and membrane structure being the unsymmetrical structure of having puncturing of micron order from submicron one in a dialysing fluid side (outside surface of a hollow filament), further It is apprehensive about the endotoxin invasion from this big aperture, and is only that a detached core with a thickness of several [a little less than (3 microns or less)] microns is shown in an internal surface, and the probability for endotoxin to invade into blood only by producing some defects in this layer becomes high.
[0012] The method of processing the film to JP,7-116484,A by cationic resin, and making endotoxin stick to it by the interaction like ion as a technique which gives endotoxin adsorption capacity to the polysulfone system film itself is indicated. However, it is not necessarily anion-like [all the components of endotoxin], and is a question about the effectiveness under high electrolytic concentration, such as dialysing fluid and blood. Moreover, for using as blood purification film, it is not necessarily applicable from the field of the safety of the membraneous ability fall by the cation resin coat, an effluent, etc.
[0013] Moreover, as selective adsorbent of endotoxin, although there is a histidine bridging (446 a fermentation engineering meeting magazine, 65 volumes, No. 5, 1987) or a polymyxin bridging (JP,5-305139,A), these are the technique for carrying out adsorption treatment of the endotoxin content liquid by direct perfusion, and are not the techniques applied to the blood purification film as used in the field of this invention.
[0014]
[Problem(s) to be Solved by the Invention] Although the technical problem of this invention is excellent in the removal engine performance of harmful low-molecular protein, such as beta 2-

microglobulin, at the time of blood purification, it is to provide a blood side with the blood purification film which does not pass endotoxin substantially and which has the high dialysis engine performance and high safety from a dialysing fluid side.
[0015] Although invention-in-this-application persons removed unnecessary low-molecular protein from the blood side to the dialysing fluid side by making the configuration polymer ratio of the hydrophobic macromolecule of the film whole region of a hollow fiber, and a hydrophilic macromolecule into the suitable range, and giving moderate hydrophilic property and hydrophobicity to the whole hollow fiber as a result of inquiring wholeheartedly, in order to solve this technical problem, it found out that it became possible to lose contamination of the endotoxin from a dialysing fluid side to a blood side. Furthermore, it found out that endotoxin could be prevented by the whole film by [which include neither a void nor the network structure for the membrane structure of a hollow fiber] considering as uniform structure substantially.
[0016] moreover -- the macromolecule which has aromatic series as a functional group -- endotoxin adsorption capacity -- it is -- ** -- it found out that the pollution control by endotoxin could be attained further easily by constituting a hollow fiber with the macromolecule of an aromatic series system [like]. ** -- endotoxin originates in the lipid section of endotoxin joint protein or lipid A, and it is thought of because it has adsorbent in a hydrophobic side to some extent that endotoxin sticks to the macromolecule of an aromatic series system [like].
[0017] Furthermore, in order to reconcile the permeability of the low-molecular protein field (a little less than 20,000 molecular weight) which is the need property of above HPM, and advanced endotoxin removal, this invention persons developed the pore control technique by the side of the dialysing fluid which cannot be accomplished by the conventional blood purification film (hollow filament outside). This also gave a compact layer and pore to the hollow filament external surface of homogeneous membrane structure, and it found out that endotoxin could be adsorbed by the large adsorption area of the whole thickness section also to the endotoxin which invaded into control of invasion of the endotoxin from hollow filament external surface, adsorption, and the pore section that performs solute transparency further.
[0018] In case the spinning undiluted solution with which pore control of hollow filament external surface was breathed out from the nozzle in the hollow filament spinning process by the aforementioned phase separation method is deliquored from hollow filament external surface in a coagulation bath, dedropping and what has the still more unstable stagnation to hydrophobic **** by processing of rinsing etc. are slightly dropped completely for the hydrophilic macromolecule near the outside surface by coincidence into a coagulation bath. The omission section of this hydrophilic giant molecule forms the detailed hole below submicron one in the membranous outside-surface section, and is considered with the ability of the adsorption capacity of endotoxin to be made to increase according to the activated carbon-effectiveness by this pore.
[0019] Evaluation of the pore of an outside surface has the possibility of a certain amount of observation with SEM, an atomic force microscope, a replica method, etc. However, even if observation in the condition (KURAIO SEM, the low vacuum (SEM) in the thing made to freeze-dry or the condition of having got wet) except the point that the hollow filament is covered by the film structure-preserving agent, and a ******** membrane structure hold-back agent is possible, in current technology, it is thought that the exact surface pore evaluation below submicron one is difficult. Moreover, although there is an appraisal method of the pore by the BET adsorption method and the method of mercury penetration itself, these are impossible for evaluation of a local part called only a front face. Although this invention persons examined seeing the abundance of the hydrophilic macromolecule on the front face of the outermost by the

surface IR method as indirect evaluation, since the problem of precision and the information on several micrometer depth were intermingled, difference evaluation of a minute amount was difficult. According to the above circumstances, this invention persons came to develop the blood purification film which it had [film] the solute permeability as HPM, and realized coexistence of adsorbent [over endotoxin], and invasion inhibition.
[0020] This invention completes examination in piles further based on the above-mentioned knowledge.
[0021] That is, the invention in this application offers the hollow fiber with which the content of a hydrophobic macromolecule is the hollow fiber which is 95 - 80 % of the weight, and the content of the hydrophilic macromolecule to the ** (hydrophobicity and hydrophilic property) macromolecule which constitutes a hollow fiber fills the formula of the following [content / (for A % and an outside surface, B % and film pars intermedia are / an internal surface / C %) / of the hydrophilic macromolecule in the internal surface, outside surface, and film pars intermedia of this hollow fiber] five to 20% of the weight.
(A-X) 0.5 / X<=0.5, however X= (A+B+C)/3 (2+(B-X) 2+(C-X) 2) [0022] In a suitable embodiment, when observing the film cross section of said hollow fiber with a 300 times as many electron microscope as this, the void or the network structure accepted clearly does not exist, but the internal structure of said hollow fiber is homogeneity structure substantially.
[0023] In a suitable embodiment, when observing the internal surface and outside surface of said hollow fiber with a 5000 times as many electron microscope as this, the hole accepted clearly does not exist but the surface structure of said hollow fiber is smooth structure substantially.
[0024] It is 2 1m by the internal-surface conversion filled up with said hollow fiber in the suitable embodiment. The sieve multiplier of the beta 2-microglobulin in bovine blood liquid when filtering bovine blood liquid with a protein concentration of 7g [/ml] by part for 200ml/of the rates of flow hematocrit 30% to a module by part for sink and 10ml/of the filtration rates of flow is 50% or more.
[0025] In a suitable embodiment, said hydrophobic macromolecule is an aromatic series polysulfone system macromolecule.
[0026] In a suitable embodiment, said hydrophilic giant molecule is a polyvinyl pyrrolidone.
[0027] In a suitable embodiment, said hollow fiber contains polyhydric alcohol as a film structure-preserving agent.
[0028] Hereafter, the invention in this application is explained to a detail.
[0029] Although the hydrophobic giant molecule used for the hollow fiber of this invention is not limited to which thing of a cellulose system, a vinyl system, and an aromatic series system, the giant molecule of an aromatic series system with adsorbent [over endotoxin / comparatively high], for example, an aromatic series polysulfone system giant molecule, an aromatic polyamide system giant molecule, an aromatic polyimide system giant molecule, an aromatic series polyether system giant molecule, an aromatic polyester system giant molecule, an aromatic series poly ketone system giant molecule, its aromatic series poly sulfate system giant molecule, etc. are desirable. The viewpoint of hollow filament workability, film production nature, and biocompatibility to especially an aromatic series polysulfone system macromolecule is still more desirable. In addition, it is not limited especially if the above-mentioned aromatic series polysulfone system macromolecule is a polysulfone system macromolecule which has an aromatic series functional group in a molecule, and aromatic series polysulfone, aromatic series polyether sulphone, etc. are mentioned.
[0030] The synthetic macromolecule with which the hydrophilic giant molecule used for the

hollow fiber of this invention consists of polyvinyl alcohol, a polyethylene glycol, a polypropylene glycol, a polyvinyl pyrrolidone, polyethyleneimine, those copolymers, etc., or polysaccharide is mentioned. Viewpoints, such as compatibility with the above-mentioned hydrophobic giant molecule and film production nature, to especially a polyvinyl pyrrolidone is still more desirable also in this.

[0031] The content of a hydrophobic macromolecule of the content of the hydrophilic macromolecule in the ** (hydrophobicity and hydrophilic property) macromolecule which constitutes the hollow fiber of this invention is 95 - 80 % of the weight five to 20% of the weight. When the content of a hydrophilic macromolecule is less than 5 % of the weight, sufficient solute permeability as HPM which makes endotoxin adsorbent the purpose of this invention of a certain thing is not acquired. When the content of a hydrophilic macromolecule exceeds 20 % of the weight, possibility that a hydrophilic macromolecule will be eluted becomes high and becomes a problem from a safety aspect. The content of a desirable hydrophilic macromolecule is 8 - 20 % of the weight, and especially desirable content is 12 - 16 % of the weight.

[0032] In addition, a hollow filament can be ground, and it can equalize, or a suitable solvent can be made to be able to carry out the homogeneity dissolution, and the content of the hydrophilic macromolecule of the whole film can measure the content of a hydrophilic macromolecule by technique, such as elemental analysis, molecular vibration analysis, and NMR, after making only the macromolecule material which constitutes the film except for a film structure-preserving agent by suitable processings (rinsing, desiccation, etc.) boiled. When carrying out by elemental analysis, it asks for the content of the element which exists only in a hydrophilic macromolecule or a hydrophobic macromolecule, and asks for the content of one of the whole macromolecules from the molecular structure. In molecular vibration analysis (for example, IR analysis) and NMR, it can ask for content from reinforcement, such as an absorption band peculiar to a hydrophilic giant molecule or a hydrophobic giant molecule, and a chemical shift. Although it could ask for the content of a hydrophilic macromolecule by any aforementioned approach, in this invention, the content of the hydrophilic macromolecule of the whole film was measured by IR analysis. The detail of a measuring method is as given in the column of measurement of the content of the hydrophilic macromolecule of the whole film.

[0033] Moreover, the hollow fiber of this invention fills the formula of the following [content / (for A % and an outside surface, B % and film pars intermedia are / an internal surface / C %) / of the hydrophilic macromolecule in an internal surface, a membranous outside surface, and membranous film pars intermedia].

(A-X) 0.5 / X<=0.5, however X= (A+B+C)/3 -- when the value of this formula exceeds 0.5, it becomes the macromolecule presentation which inclined toward the hydrophilic macromolecule or the hydrophobic macromolecule, and adsorbent [of endotoxin] falls (2+(B-X) 2+(C-X) 2). Moreover, that the value of this formula is 0.5 or less has compactness with the whole moderate film, and it can prevent endotoxin by the whole film. The value of a desirable formula is 0.4 or less. In addition, the distribution condition of the hydrophilic macromolecule of (an internal surface, an outside surface, and pars intermedia) is shown, a hydrophilic macromolecule is distributed at least over each part by at least membranous each part at homogeneity, so that the value of this formula is small, this formula shows that that content is also fixed, distribution of the hydrophilic macromolecule like each part is so uneven that the value of this formula is large, and it is shown that a big difference is in the content of the hydrophilic macromolecule like each part. Henceforth, let the value of this formula be a hydrophilic macromolecule distribution

number.
[0034] In addition, the content of the hydrophilic macromolecule like membranous each part can be evaluated from various energy and molecular vibration analysis based on the surface analysis technique. In this invention, the content of the hydrophilic giant molecule of an about [each part] is measured from the ratio of the band strength originating in the hydrophilic giant molecule contained in a membranous internal surface, pars intermedia, and an outside surface by micro Fourier transform infrared spectrophotometry, and a hydrophobic giant molecule. The detail of a measuring method is as given in the column of measurement of the content of the hydrophilic macromolecule like membranous each part.
[0035] When the hollow fiber of this invention observes a membranous cross section with a 300 times as many electron microscope as this, the void accepted clearly or the network structure does not exist. that the void accepted clearly or the network structure does not exist above when observing a membranous cross section with a 300 times as many electron microscope as this is the homogeneity structure where a film internal structure does not have a cavity substantially -- meaning -- ** -- the hollow fiber of this invention becomes possible [preventing migration of the endotoxin from a dialysing fluid side to a blood side by the whole film] by being homogeneity structure like.
[0036] When the hollow fiber of this invention observes a membranous internal surface and a membranous outside surface with a 5000 times as many electron microscope as this, the hole accepted clearly does not exist. If the hole accepted clearly does not exist when observing a membranous internal surface and a membranous outside surface with a 5000 times as many electron microscope as this a membranous surface structure is smooth structure substantially -- meaning -- ** -- the hollow fiber of this invention by being smooth structure like Also when actually processing blood, there is little blinding of a hole, and a secondary polarization layer will also be formed thinly and becomes possible [maintaining the high removal engine performance of unnecessary low-molecular protein, such as beta 2-microglobulin,].
[0037] In addition, generally, evaluation by the scanning electron microscope (SEM) is a stock-in-trade, and membrane structure evaluated membrane structure based on observation by the electron microscope also in this application. In addition, the membrane structure of this invention is homogeneity and smooth structure substantially as they were explained above. ** -- in order to evaluate homogeneity and smooth nature, it should observe and the electron microscope of the biggest original possible scale factor should estimate, but in order to avoid the effect on the membrane structure by the heat which an electron microscope generates, in the present condition, 5000 times are an upper limit. [like] Therefore, in this application, evaluation of membranous smooth nature was evaluated by observing the internal surface and outside surface of a hollow fiber with a 5000 times as many electron microscope as this. Here, when a hole did not exist and the observation limit in a 5000 times as many enlargement as this sets to 0.2mm, it means that a hole or a cavity 400A or more do not exist.
[0038] Thickness is several micrometers - 80 micrometers, and, as for the hollow fiber of this invention, it is desirable to have the cross section of the perfect circle form where an outer diameter is 100 micrometers - 500 micrometers. As described above, since the hollow fiber of this invention is homogeneity structure substantially, to lower thickness to raising the separation efficiency of a solute is desired, thickness is 15 micrometers - 40 micrometers preferably, and an outer diameter is 200-300 micrometers.
[0039] It is 2 1m by the internal-surface conversion filled up with the hollow fiber of this invention. The sieve multiplier of the beta 2-microglobulin in bovine blood liquid when filtering

bovine blood liquid with a protein concentration of 7g [/ml] by part for 200ml/of the rates of flow hematocrit 30% to a module by part for sink and 10ml/of the filtration rates of flow is 50% or more. 50% or less of the elimination factor of beta 2-microglobulin is [a sieve multiplier] insufficient. Moreover, in this invention, the elimination factor at the time of actually pouring blood as mentioned above prescribed the elimination factor of beta 2-microglobulin. This is for forming a secondary polarization layer as mentioned above, and producing a big difference by the sieve multiplier in a drainage system, and the sieve multiplier in a blood system, when blood is actually poured to a hollow fiber.

[0040] Moreover, it is defined as 50% or more of permeability here by the sieve multiplier (SC) shown by the following formula using the liquid which penetrated the liquid supplied to a hollow filament, the passed liquid, and the film, and the beta 2-microglobulin concentration contained in each.

Beta 2-microglobulin concentration T3 in SC(%) =(T1x2)/(T2+T3) x100, however the beta 2-microglobulin concentration T2:supply liquid in T1:permeate liquid: Beta 2-microglobulin concentration in passage liquid [0041] As for the hollow fiber of this invention, it is desirable that membrane structure is held by the film structure-preserving agent. As for a film structure-preserving agent, it is desirable that it is necessary to be the matter easily washed and removed with water, a physiological saline, etc. in case it is used as blood purifier, and it is the water-soluble matter. For example, polyhydric alcohol, such as glycerol and a glycol, polysaccharide, or a surfactant is mentioned. Especially, installation the safety as blood purification film and inside [of polysulfone system homogeneous membrane] pore is especially easy for a glycerol, and is desirable.

[0042] As an approach of creating the hollow filament mold blood purification film of this invention, a hydrophobic macromolecule and a hydrophilic macromolecule are dissolved in the solvent which consists of mixed liquor of a solvent or a solvent, and a poor solvent, for example, a dope undiluted solution is prepared, and the method of making this breathe out from a nozzle and making the film formation by phase separation perform in coagulation liquid is mentioned. By this approach, pore size distribution of membranous pore is narrowed and it becomes possible to acquire the fractionation property of a sharp constituent of blood. Moreover, it is possible by choosing suitable dope conditions and coagulation conditions to give various solute separation properties to the film.

[0043] Moreover, it is required for formation of a centrum to use a centrum formation heart agent, and this heart agent may be used for coincidence as coagulation liquid. By the film of the conventional polysulfone system, the asymmetric membrane which the film is produced by this technique and the inside solidified densely is formed. Homogeneous membrane can be obtained by using gas or the fluid of low freezing characteristic for a heart agent to it. When gas etc. is furthermore used for a heart agent to what a hydrophilic macromolecule tends to carry out localization to a compact layer in in the case of unsymmetrical structure, a hydrophilic macromolecule can be comparatively introduced into the whole film at homogeneity, and it becomes possible to obtain the film which has the good structure of the balance of a hydrophilic property and hydrophobicity by the whole film.

[0044] The hollow fiber furthermore formed processes rinsing, desiccation, etc. The homogeneous membrane which does not have supporters at this desiccation process has much fall ****** in the membraneous ability which the film contracted with the surface tension of the water accompanying desiccation etc., and was prepared by the phase separation method. In order to prevent this, it is desirable to include a film structure-preserving agent in membrane structure.

As for a film structure-preserving agent, being introduced before a desiccation process is optimal after rinsing.

[0045] The hollow filament mold blood purification film of this invention can specifically, for example, as follows, be manufactured.

[0046] The spinning undiluted solution containing 2 - 5 % of the weight of hydrophilic macromolecules, 30 - 60 % of the weight of solvents, and 10 - 50 % of the weight of non-solvents is heated and dissolved in 50-190 degrees C 35% of the weight from the hydrophobic macromolecule 15, and it extrudes from the outside of a double pipe nozzle, and from a center, there is no freezing characteristic to a gas or a spinning undiluted solution, or the low liquid of freezing characteristic is sent in. After it passes through the inside of 40 - 60% of the weight of a glycerol water solution after it was solidified through the 5-60-degree C freezing characteristic liquid after the extruded spinning undiluted solution made it run the 1-20mm air, and it was rinsed, and it infiltrates a glycerol, it is dried with a dryer.

[0047] As the above-mentioned solvent, polar solvents, such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methyl pyrrolidone, and gamma-butyrolactone, can be used by independent or mixing. independent [in ether, such as polyols, such as ethylene glycol, triethylene glycol, a polyethylene glycol, a propanediol, and butanediol, or ethylene glycol monoethyl ether, and diethylene glycol monoethyl ether,] as the above-mentioned non-solvent -- or it can be mixed and used. Moreover, as a hollow formation agent, fats and oils, such as gas, such as nitrogen, an argon, oxygen, carbon dioxide gas, helium, and air, or a liquid paraffin, myristic-acid isopropyl, vegetation, and straight mineral oil, or other low freezing characteristic liquids can be used. The solvent which can be used by this invention, a non-solvent, and a hollow formation agent are not restricted above.

[0048] Hereafter, although an example explains the contents of this invention to a detail further, this invention is not limited at all by the following.

[0049] First, the measuring method of the beta 2-microglobulin of the blood purification film of this invention, endotoxin, an effluent, and a hydrophilic macromolecule content is explained.

[0050] 1. By the internal-surface conversion in which put in the hollow filament of about 10000 SC(%) trial blood purification film of beta 2-microglobulin into the plastic part, and both ends carried out opening, it is 2 a film area of about 1m. A module is produced. The hematocrit 30% cow fresh blood which carried out anticoagulation processing of this module after washing by the physiological saline and at a blood side (hollow filament inside) is poured by part for 200ml/. By modular internal-surface conversion, it is 2 1m of film surface products. The pump connected to the dialysing fluid side so that it might become a part for filtration velocity/of 10ml of a hit performs hemofiltration, and measurement and the aforementioned SC (%) are calculated about the following. The blood of the inlet port of the module at the time and an outlet and filtrate are sampled for hemofiltration initiation 15 minutes, and the concentration of beta 2-microglobulin is measured with enzyme immunoassay (for example, beta2-MG-EIA TEST Wako Pure Chem industry) etc. In addition, it carries out to the bovine blood liquid used by the measurement concerned by adding the beta 2-microglobulin of the Homo sapiens origin beforehand. According to a formula 1, SC (%) is calculated from the concentration of these beta 2-microglobulin.

[0051] 2. By outside-surface conversion of the hollow fiber for endotoxin adsorption test measurement, it is 2 0.05m of film surface products. A hollow fiber is minced in die length of 1cm, it puts into glassware, and 50ml of endotoxin free water is added, 30ml (about 7.0 EU/ml) of endotoxin solutions is added to the repeat last 3 times, an immersion-decantation is incubated

at 37 degrees C for 1 hour, liquid is sampled after that, and the quantum of the endotoxin is carried out. It carries out to measurement of endotoxin by the colorimetry method (Seikagaku TOKISHI color system). (Limit of detection is 0.2 EU/ml) In addition, all of the glass instrument used in this experiment, scissors, etc. use what gave 260-degree-C dry sterilization beforehand, and measurement is carried out by the clean bench.
[0052] Moreover, endotoxin removal with a module is measured by the following approaches.
[0053] 3. An endotoxin radiographic examination evaluation sample uses the same dialyzer as the above-mentioned SC (%) evaluation, and fully washes a module and the whole connection circuit by the single pass using ultrapure water (the Millipore Corp. make, milli-Q system) first. Subsequently, the liquid which flows the blood side (hollow filament inside) of a dialyzer is made into the circulatory system, and it passes by part for 200ml/(total amount of 2l. of circulating water). Circulation liquid is sampled at this time and it asks for early endotoxin concentration. Moreover, a dialyzer with a sink and a UFR controller (the Nipro make, NCU-6) is used for endotoxin content liquid (mixed water of a city water and RO water; about 2.0 EU/ml) according to a counterflow by part for 500ml/at a single pass, and the amount of water penetration between film is turned on the dialysis side to coincidence about 0. Circulating water by the side of after [2 hour progress] blood is sampled. Sampling liquid measures endotoxin concentration similarly by the aforementioned technique. The dynamic range of radiographic examination measurement of endotoxin was carried out by 0.02-0.15EU/ml. Moreover, early endotoxin concentration was below limit of detection.
[0054] 4. Measure with the ultraviolet absorption spectrum (UV) of an extract based on an eluting material test artificial-kidney acknowledgement benchmark test (Japanese artificial organ industrial association). UV of an acceptance standard is 0.1 or less.
[0055] 5. Although the content of the measurement hydrophilic-property macromolecule of the content of the hydrophilic macromolecule of the whole film and a hydrophobic macromolecule is almost the same as the preparation ratio of a spinning undiluted solution or became some fall in this invention, the check of the abundance ratio after hollow filament formation was performed by the following approaches. The KBr tablet after dissolving in a suitable solvent at homogeneity is made to apply and dry a hollow filament, and Transparency IR is measured. This estimates the peak intensity ratio of the hydrophilic macromolecule origin of IR band, and the hydrophobic macromolecule origin. The compounding ratio (% of the weight) of a hydrophilic macromolecule and a hydrophobic macromolecule measures similarly with a known sample, creates a calibration curve, and, thereby, calculates the content (weight [of a hydrophilic macromolecule] % to an overall-height molecule) of the hydrophilic macromolecule in a hollow filament.
[0056] 6. Assay of the measurement hydrophilic-property macromolecule of the content of the hydrophilic macromolecule like membranous each part measures the front face IR of the inside and an outside about the sample which cut the hollow filament perpendicularly and extended it. Pars intermedia is similarly measured about the sample which shaved off the surface and exposed pars intermedia. Pars intermedia was mostly used as the central part of the thickness section. The front face IR was performed by the FT-IR micro ATR method (IER; diamond). On this condition, about 1.5-micrometer layer on the front face of a sample is measured. Peak intensity was measured similarly and it asked for the intensity ratio. However, in this case, since the estimate of the content by calibration-curve creation was difficult, it estimated the content of a membranous internal surface, an outside surface, and the hydrophilic macromolecule in pars intermedia from the ratio of the peak intensity ratio itself. Since a **** bee and this intensity

ratio expressed the content by which the hydrophilic macromolecule like each part and the hydrophobic macromolecule were standardized, they computed the membranous hydrophilic macromolecule distribution number using this value.

[0057] Polyether sulphone 22 % of the weight, 3.0 % of the weight (K-90) of polyvinyl pyrrolidones, (Example 1) A N-methyl-2-pyrrolidone as a solvent the solution which carried out the heating dissolution of the raw material with which polyethylene-glycol #200 consist of 37.5 % of the weight at 120 degrees C as a non-solvent 37.5% of the weight Nitrogen is sent in and it considers as the shape of a hollow filament, and water, a N-methyl-2-pyrrolidone, and polyethylene-glycol #200 passed the inside of the freezing characteristic liquid with a temperature of 40 degrees C which mixes and changes by the weight ratio of 60:20:20, and made it to extrude from the outside of a double pipe nozzle and solidify from a core. Then, rinsed, after infiltrating 50% of the weight of a glycerol, it was made to dry with a dryer, and the bore of 201 micrometers and the hollow fiber of 28 micrometers of thickness were obtained. The void from a 300 time SEM image or the network structure of the cross section of the obtained hollow filament is not observed, but the hole from a 5000 time SEM image on the front face of inside and outside is checked, and it is **********. The content of the hydrophilic macromolecule from IR analysis was about 12%. The intensity ratio of an inside, a middle lamella, and an outside hydrophilic macromolecule was an outside > medium-rise > inside, and the distribution number was 0.21. Although this showed drawing 1 , drawing 2 , and drawing 3 to the example of measurement of a front face IR, it was calculated from the intensity ratio (A1670/A1570) of carbonyl absorption of the polyvinyl pyrrolidone of 1670cm-1, and absorption of the aromatic series of the polyether sulphone of 1570cm-1. In the following examples and examples of a comparison, it measured similarly. SC (%) of the beta 2-microglobulin of this hollow filament was 73%, and in an endotoxin adsorption test, the endotoxin concentration by the side of blood of the endotoxin concentration of the liquid after immersion is below limit of detection below limit of detection, and, as for most invasion by the side of the blood of endotoxin, it did not have an endotoxin radiographic examination in a module, either. Moreover, the eluting material test passed with UV=0.04.

[0058] Polyether sulphone 21 % of the weight, 3.5 % of the weight (K-90) of polyvinyl pyrrolidones, (Example 2) A N-methyl-2-pyrrolidone as a solvent the solution which carried out the heating dissolution of the raw material with which triethylene glycol consists of 37.75 % of the weight at 120 degrees C as a non-solvent 37.75% of the weight Nitrogen is sent in and it considers as the shape of a hollow filament, and water, a N-methyl-2-pyrrolidone, and triethylene glycol passed the inside of the freezing characteristic liquid with a temperature of 40 degrees C which mixes and changes by the weight ratio of 60:20:20, and made it to extrude from the outside of a double pipe nozzle and solidify from a core. Then, rinsed, after infiltrating 50% of the weight of a glycerol, it was made to dry with a dryer, and the bore of 202 micrometers and the hollow fiber of 32 micrometers of thickness were obtained. The void from a 300 time SEM image or the network structure of the cross section of the obtained hollow filament is not observed, but the hole from a 5000 time SEM image on the front face of inside and outside is checked, and it is **********. The content of the hydrophilic macromolecule from IR analysis was about 14%. The intensity ratio of an inside, a middle lamella, and an outside hydrophilic macromolecule was an outside > medium-rise > inside, and the distribution number was 0.11. SC (%) of the beta 2-microglobulin of this hollow filament was 75%. In the endotoxin adsorption test, the endotoxin concentration of the liquid after immersion is 0.5 EU/ml, and adsorption was seen. The endotoxin concentration by the side of blood is below limit of detection, and most

invasion by the side of the blood of endotoxin did not have an endotoxin removal trial with a module, either. Moreover, the eluting material test passed with UV=0.08.
[0059] Polyether sulphone 27 % of the weight, 1.0 % of the weight (K-90) of polyvinyl pyrrolidones, (Example 1 of a comparison) A N-methyl-2-pyrrolidone as a solvent the solution which carried out the heating dissolution of the raw material with which polyethylene-glycol #200 consist of 36.0 % of the weight at 120 degrees C as a non-solvent 36.0% of the weight Nitrogen is sent in and it considers as the shape of a hollow filament, and water, a N-methyl-2-pyrrolidone, and polyethylene-glycol #200 passed the inside of the freezing characteristic liquid with a temperature of 40 degrees C which mixes and changes by the weight ratio of 60:20:20, and made it to extrude from the outside of a double pipe nozzle and solidify from a core. Then, rinsed, after infiltrating 50% of the weight of a glycerol, it was made to dry with a dryer, and the bore of 201 micrometers and the hollow fiber of 28 micrometers of thickness were obtained. The void from a 300 time SEM image or the network structure of the cross section of the obtained hollow filament is not observed, but the hole from a 5000 time SEM image on the front face of inside and outside is checked, and it is **********. The content of the hydrophilic macromolecule from IR analysis was about 3.5%. The intensity ratio of an inside, a middle lamella, and an outside hydrophilic macromolecule was an outside > medium-rise = inside, and the distribution number was 0.14. SC (%) of the beta 2-microglobulin of this hollow filament is 25%, and did not satisfy the requirements for HPM. In the endotoxin adsorption test, the endotoxin concentration of the liquid after immersion is 0.2 or less EU/ml, and adsorption was seen. The endotoxin concentration by the side of blood is below limit of detection, and most invasion by the side of the blood of endotoxin did not have an endotoxin removal trial with a module, either. Moreover, the eluting material test passed with UV=0.02.
[0060] Polyether sulphone 25 % of the weight, 5.0 % of the weight (K-90) of polyvinyl pyrrolidones, (Example 2 of a comparison) A N-methyl-2-pyrrolidone as a solvent the solution which carried out the heating dissolution of the raw material with which polyethylene-glycol #200 consist of 35.0 % of the weight at 120 degrees C as a non-solvent 35.0% of the weight It extrudes from the outside of a double pipe nozzle. From a core Pour water, a N-methyl-2-pyrrolidone, and the liquid of freezing characteristic with which polyethylene-glycol #200 mix and change by the weight ratio of 60:20:20, and it considers as the shape of a hollow filament. Water, a N-methyl-2-pyrrolidone, and polyethylene-glycol #200 passed the inside of the freezing characteristic liquid with a temperature of 40 degrees C which mixes and changes by the weight ratio of 60:20:20, and made it solidify. Then, rinsed, after infiltrating 50% of the weight of a glycerol, it was made to dry with a dryer, and the bore of 201 micrometers and the hollow fiber of 40 micrometers of thickness were obtained. The network structure from a 300 time SEM image of the cross section of the obtained hollow filament was observed, and the hole from a 5000 time SEM image of an outside surface was checked, and it was not homogeneous membrane but asymmetric membrane. The content of the hydrophilic macromolecule from IR analysis was 5.0%. The intensity ratio of an inside, a middle lamella, and an outside hydrophilic macromolecule was an outside < medium-rise < inside, and the distribution number was 0.74. SC (%) of the beta 2-microglobulin of this hollow filament is 45%, and did not satisfy the requirements for HPM. In the endotoxin adsorption test, the endotoxin concentration of the liquid after immersion is 2.5 EU/ml, and adsorption was seen. In the endotoxin removal trial with a module, the endotoxin concentration by the side of blood is 0.15 or more EU/ml, and the invasion by the side of the blood of endotoxin was seen. Moreover, eluting material tests were UV=0.11 and a rejection.

[0061]
[Table 1]

[0062]
[Effect of the Invention] The hollow fiber of this invention has the penetrable high ability which can remove beta 2-microglobulin 50% or more in the system which actually pours blood, prevents contamination of the endotoxin by the side of blood, and has adsorbent [high] and inhibition nature to TOSHIN so that clearly from the above explanation. ** -- like, in the medical fields, such as hemodialysis, especially HPM, etc., it has the removal engine performance of a higher undesired substance, and the hollow fiber of this invention has higher safety, and enables the therapy of advanced quality by the hollow fiber of the invention in this application. As above, the effectiveness of the hollow fiber of this invention is size, and the use will be expected very much from now on in fields, such as hemodialysis which reclaims the improvement to dialysis complication from a new index.

TECHNICAL FIELD

[Field of the Invention] This invention relates to the hollow fiber used for blood purification etc. as an artificial organ. Also when endotoxin is contained in a dialysing fluid side in blood purification etc. in more detail, maintaining the high removal engine performance of low-

molecular protein, such as beta 2-microglobulin, it is related with the hollow fiber which does not make the endotoxin invade into a blood side substantially.

PRIOR ART

[Description of the Prior Art] From the former, the permeable membrane and ultrafiltration membrane using a polymer, such as a cellulose, cellulose acetate, polymethylmethacrylate, and a polyacrylonitrile, are used in the medical field for the purpose which removes the wastes in blood. The cellulose wall has been especially used widely in the dialysis treatment for the prolongation of life and social rehabilitation of a renal failure patient.

[0003] For the purpose of removing low-molecular matter, such as a urea in blood, and a creatinine, it has been developed and clinical supply of these film has been carried out at the beginning. However, it is required for these blood purification film that the quality of a removal object by dialysis should make not only low-molecular matter, such as a urea and a creatinine, but the matter (low-molecular protein) of inside molecular weight to the amount of macromolecules applicable to removal in recent years with the increment in a long-term dialysis patient by long-term dialysis complication, such as a carpal tunnel syndrome, coming to attract attention. The film used for these therapies is called the high performance film (following, HPM), and enables removal of the bigger matter by expanding a membranous aperture from the conventional permeable membrane.

[0004] It becomes right and wrong of the engine performance of HPM how fractionation of the albumin (molecular weight of 66000dalton) which is the useful protein in blood is performed to Sharp by the high polymer for [which attracts attention especially on clinical] removal being beta 2-microglobulin (molecular weight of 11600dalton) considered to be the quality of an amyloid ghost which causes a carpal tunnel syndrome, and excelling in the removal nature of beta 2-microglobulin.

[0005] To this problem, the conventional cellulose wall cannot necessarily say it as the material which can give the optimal membrane structure, but the material of synthetic systems, such as a cellulose triacetate, a polyacrylonitrile, and polysulfone, serves as a subject in this HPM field. Especially, the transparency film of a polysulfone system is excellent in the fabrication nature of a hollow fiber, and film production nature, and the film which suppressed the fall of solute permeability by the hydrophobicity of the polysulfone itself is indicated by JP,61-93801,A and JP,4-300636,A by blending a hydrophilic giant molecule.

[0006] Furthermore, the interleukin assumption (3 Blood Purif., 1; 1983) which Henderson and others to long-term dialysis complication presented is regarded as questionable with the spread of HPM(s) in recent years. according to this idea, as an immunity-process which causes the dialysis amyloidosis, monocyte is stimulated by activation of complement, the endotoxin in blood acts there, and the interleukin (IL-1) from monocyte carries out production emission -- having -- it -- growth of fibrocyte or a collagen -- starting -- moreover, manifestation sthenia of the human leucocyte antigen class 1 -- beta 2-microglobulin emission -- causing -- the amyloid to arthritis and a bone -- resulting in the self-possessed onset is shown. In a long-term dialysis patient, there is a chronic IL-1 production stimulus by activation of permeable membrane and the complement by contact of blood, extracorporeal circulation enforcement (invasion into the blood of the endotoxin from dialysing fluid etc.) of blood, etc., and it results in complication.

[0007] To this problem, a cellulose triacetate, polysulfone, etc. are known as a material of good biocompatibility (low complement activity). However, in HPM, since the film aperture is made

to expand, to invasion of the endotoxin from the outside, a result by which dangerous ** is carried out conversely has been brought.

[0008] Moreover, in HPM, in the blood inflow section of blood purifier, a blood side becomes negative pressure from the effect of the pressure loss of the hemodialyzer, and the osmotic pressure difference of blood-dialysing fluid near a blood outlet in spite of positive pressure, it is known that the 'Backfiltration' phenomenon which the reverse filtration from a dialysing fluid side produces will happen, and it is apprehensive about the danger of endotoxin invasion into blood also from this point. It is actually reported by the patient group of cellulose wall use, and the patient group of synthetic membrane use of a HPM system that latter one has a high rate of endotoxin antibody-positive. (Trans.Am.Soc.Artif.Inten.Organs,35;331,1989)

[0009] Endotoxin is the lipopolysaccharide or its protein complex of the cell wall origin of a gram negative, the minimum fragmentation which has activity is lipid A, and molecular weight is thousands here. Therefore, endotoxin will be penetrated for HPM with 10,000 cuts off molecular weight. The polysulfone hollow fiber currently similarly indicated as the aforementioned conventional technique cannot guarantee the nontransparent nature of endotoxin, either. on the other hand, the time of clinical use -- endotoxin -- although using free dialysing fluid is recommended, current is impossible without the thorough validation of the whole dialysis facility which there is disadvantageous profit to which equipment and a running cost increase, and also included people's activity in carrying out an endotoxin free-lancer completely.

[0010] Moreover, preparing an endotoxin removal filter just before the blood purifier of the supply line of dialysing fluid is also performed. However, there is also a report that endotoxin is condensed by the connection to blood purifier, and having the function in which the blood purifier itself does not make endotoxin invade, finally can call it an ideal.

[0011] On the other hand, the polysulfone film currently indicated as the aforementioned conventional technique first of all, from there being no description to endotoxin and membrane structure being the unsymmetrical structure of having puncturing of micron order from submicron one in a dialysing fluid side (outside surface of a hollow filament), further It is apprehensive about the endotoxin invasion from this big aperture, and is only that a detached core with a thickness of several [a little less than (3 microns or less)] microns is shown in an internal surface, and the probability for endotoxin to invade into blood only by producing some defects in this layer becomes high.

[0012] The method of processing the film to JP,7-116484,A by cationic resin, and making endotoxin stick to it by the interaction like ion as a technique which gives endotoxin adsorption capacity to the polysulfone system film itself is indicated. However, it is not necessarily anion-like [all the components of endotoxin], and is a question about the effectiveness under high electrolytic concentration, such as dialysing fluid and blood. Moreover, for using as blood purification film, it is not necessarily applicable from the field of the safety of the membraneous ability fall by the cation resin coat, an effluent, etc.

[0013] Moreover, as selective adsorbent of endotoxin, although there is a histidine bridging (446 a fermentation engineering meeting magazine, 65 volumes, No. 5, 1987) or a polymyxin bridging (JP,5-305139,A), these are the technique for carrying out adsorption treatment of the endotoxin content liquid by direct perfusion, and are not the techniques applied to the blood purification film as used in the field of this invention.

EFFECT OF THE INVENTION

[Effect of the Invention] The hollow fiber of this invention has the penetrable high ability which can remove beta 2-microglobulin 50% or more in the system which actually pours blood, prevents contamination of the endotoxin by the side of blood, and has adsorbent [high] and inhibition nature to TOSHIN so that clearly from the above explanation. ** -- like, in the medical fields, such as hemodialysis, especially HPM, etc., it has the removal engine performance of a higher undesired substance, and the hollow fiber of this invention has higher safety, and enables the therapy of advanced quality by the hollow fiber of the invention in this application. As above, the effectiveness of the hollow fiber of this invention is size, and the use will be expected very much from now on in fields, such as hemodialysis which reclaims the improvement to dialysis complication from a new index.

TECHNICAL PROBLEM

[Problem(s) to be Solved by the Invention] Although the technical problem of this invention is excellent in the removal engine performance of harmful low-molecular protein, such as beta 2-microglobulin, at the time of blood purification, it is to provide a blood side with the blood purification film which does not pass endotoxin substantially and which has the high dialysis engine performance and high safety from a dialysing fluid side.

[0015] Although invention-in-this-application persons removed unnecessary low-molecular protein from the blood side to the dialysing fluid side by making the configuration polymer ratio of the hydrophobic macromolecule of the film whole region of a hollow fiber, and a hydrophilic macromolecule into the suitable range, and giving moderate hydrophilic property and hydrophobicity to the whole hollow fiber as a result of inquiring wholeheartedly, in order to solve this technical problem, it found out that it became possible to lose contamination of the endotoxin from a dialysing fluid side to a blood side. Furthermore, it found out that endotoxin could be prevented by the whole film by [which include neither a void nor the network structure for the membrane structure of a hollow fiber] considering as uniform structure substantially.

[0016] moreover -- the macromolecule which has aromatic series as a functional group -- endotoxin adsorption capacity -- it is -- ** -- it found out that the pollution control by endotoxin could be attained further easily by constituting a hollow fiber with the macromolecule of an aromatic series system [like]. ** -- endotoxin originates in the lipid section of endotoxin joint protein or lipid A, and it is thought of because it has adsorbent in a hydrophobic side to some extent that endotoxin sticks to the macromolecule of an aromatic series system [like].

[0017] Furthermore, in order to reconcile the permeability of the low-molecular protein field (a little less than 20,000 molecular weight) which is the need property of above HPM, and advanced endotoxin removal, this invention persons developed the pore control technique by the side of the dialysing fluid which cannot be accomplished by the conventional blood purification film (hollow filament outside). This also gave a compact layer and pore to the hollow filament external surface of homogeneous membrane structure, and it found out that endotoxin could be adsorbed by the large adsorption area of the whole thickness section also to the endotoxin which invaded into control of invasion of the endotoxin from hollow filament external surface, adsorption, and the pore section that performs solute transparency further.

[0018] In case the spinning undiluted solution with which pore control of hollow filament external surface was breathed out from the nozzle in the hollow filament spinning process by the

aforementioned phase separation method is deliquored from hollow filament external surface in a coagulation bath, dedropping and what has the still more unstable stagnation to hydrophobic **** by processing of rinsing etc. are slightly dropped completely for the hydrophilic macromolecule near the outside surface by coincidence into a coagulation bath. The omission section of this hydrophilic giant molecule forms the detailed hole below submicron one in the membranous outside-surface section, and is considered with the ability of the adsorption capacity of endotoxin to be made to increase according to the activated carbon-effectiveness by this pore.
[0019] Evaluation of the pore of an outside surface has the possibility of a certain amount of observation with SEM, an atomic force microscope, a replica method, etc. However, even if observation in the condition (KURAIO SEM, the low vacuum (SEM) in the thing made to freeze-dry or the condition of having got wet) except the point that the hollow filament is covered by the film structure-preserving agent, and a ******** membrane structure hold-back agent is possible, in current technology, it is thought that the exact surface pore evaluation below submicron one is difficult. Moreover, although there is an appraisal method of the pore by the BET adsorption method and the method of mercury penetration itself, these are impossible for evaluation of a local part called only a front face. Although this invention persons examined seeing the abundance of the hydrophilic macromolecule on the front face of the outermost by the surface IR method as indirect evaluation, since the problem of precision and the information on several micrometer depth were intermingled, difference evaluation of a minute amount was difficult. According to the above circumstances, this invention persons came to develop the blood purification film which it had [film] the solute permeability as HPM, and realized coexistence of adsorbent [over endotoxin], and invasion inhibition.
[0020] This invention completes examination in piles further based on the above-mentioned knowledge.
[0021] That is, the invention in this application offers the hollow fiber with which the content of a hydrophobic macromolecule is the hollow fiber which is 95 - 80 % of the weight, and the content of the hydrophilic macromolecule to the ** (hydrophobicity and hydrophilic property) macromolecule which constitutes a hollow fiber fills the formula of the following [content / (for A % and an outside surface, B % and film pars intermedia are / an internal surface / C %) / of the hydrophilic macromolecule in the internal surface, outside surface, and film pars intermedia of this hollow fiber] five to 20% of the weight.
(A-X) 0.5 / X<=0.5, however X= (A+B+C)/3 (2+(B-X) 2+(C-X) 2) [0022] In a suitable embodiment, when observing the film cross section of said hollow fiber with a 300 times as many electron microscope as this, the void or the network structure accepted clearly does not exist, but the internal structure of said hollow fiber is homogeneity structure substantially.
[0023] In a suitable embodiment, when observing the internal surface and outside surface of said hollow fiber with a 5000 times as many electron microscope as this, the hole accepted clearly does not exist but the surface structure of said hollow fiber is smooth structure substantially.
[0024] It is 2 1m by the internal-surface conversion filled up with said hollow fiber in the suitable embodiment. The sieve multiplier of the beta 2-microglobulin in bovine blood liquid when filtering bovine blood liquid with a protein concentration of 7g [/ml] by part for 200ml/of the rates of flow hematocrit 30% to a module by part for sink and 10ml/of the filtration rates of flow is 50% or more.
[0025] In a suitable embodiment, said hydrophobic macromolecule is an aromatic series polysulfone system macromolecule.
[0026] In a suitable embodiment, said hydrophilic giant molecule is a polyvinyl pyrrolidone.

[0027] In a suitable embodiment, said hollow fiber contains polyhydric alcohol as a film structure-preserving agent.
[0028] Hereafter, the invention in this application is explained to a detail.
[0029] Although the hydrophobic giant molecule used for the hollow fiber of this invention is not limited to which thing of a cellulose system, a vinyl system, and an aromatic series system, the giant molecule of an aromatic series system with adsorbent [over endotoxin / comparatively high], for example, an aromatic series polysulfone system giant molecule, an aromatic polyamide system giant molecule, an aromatic polyimide system giant molecule, an aromatic series polyether system giant molecule, an aromatic polyester system giant molecule, an aromatic series poly ketone system giant molecule, its aromatic series poly sulfate system giant molecule, etc. are desirable. The viewpoint of hollow filament workability, film production nature, and biocompatibility to especially an aromatic series polysulfone system macromolecule is still more desirable. In addition, it is not limited especially if the above-mentioned aromatic series polysulfone system macromolecule is a polysulfone system macromolecule which has an aromatic series functional group in a molecule, and aromatic series polysulfone, aromatic series polyether sulphone, etc. are mentioned.
[0030] The synthetic macromolecule with which the hydrophilic giant molecule used for the hollow fiber of this invention consists of polyvinyl alcohol, a polyethylene glycol, a polypropylene glycol, a polyvinyl pyrrolidone, polyethyleneimine, those copolymers, etc., or polysaccharide is mentioned. Viewpoints, such as compatibility with the above-mentioned hydrophobic giant molecule and film production nature, to especially a polyvinyl pyrrolidone is still more desirable also in this.
[0031] The content of a hydrophobic macromolecule of the content of the hydrophilic macromolecule in the ** (hydrophobicity and hydrophilic property) macromolecule which constitutes the hollow fiber of this invention is 95 - 80 % of the weight five to 20% of the weight. When the content of a hydrophilic macromolecule is less than 5 % of the weight, sufficient solute permeability as HPM which makes endotoxin adsorbent the purpose of this invention of a certain thing is not acquired. When the content of a hydrophilic macromolecule exceeds 20 % of the weight, possibility that a hydrophilic macromolecule will be eluted becomes high and becomes a problem from a safety aspect. The content of a desirable hydrophilic macromolecule is 8 - 20 % of the weight, and especially desirable content is 12 - 16 % of the weight.
[0032] In addition, a hollow filament can be ground, and it can equalize, or a suitable solvent can be made to be able to carry out the homogeneity dissolution, and the content of the hydrophilic macromolecule of the whole film can measure the content of a hydrophilic macromolecule by technique, such as elemental analysis, molecular vibration analysis, and NMR, after making only the macromolecule material which constitutes the film except for a film structure-preserving agent by suitable processings (rinsing, desiccation, etc.) boiled. When carrying out by elemental analysis, it asks for the content of the element which exists only in a hydrophilic macromolecule or a hydrophobic macromolecule, and asks for the content of one of the whole macromolecules from the molecular structure. In molecular vibration analysis (for example, IR analysis) and NMR, it can ask for content from reinforcement, such as an absorption band peculiar to a hydrophilic giant molecule or a hydrophobic giant molecule, and a chemical shift. Although it could ask for the content of a hydrophilic macromolecule by any aforementioned approach, in this invention, the content of the hydrophilic macromolecule of the whole film was measured by IR analysis. The detail of a measuring method is as given in the column of measurement of the

content of the hydrophilic macromolecule of the whole film.
[0033] Moreover, the hollow fiber of this invention fills the formula of the following [content / (for A % and an outside surface, B % and film pars intermedia are / an internal surface / C %) / of the hydrophilic macromolecule in an internal surface, a membranous outside surface, and membranous film pars intermedia].
(A-X) 0.5 / X<=0.5, however X= (A+B+C)/3 -- when the value of this formula exceeds 0.5, it becomes the macromolecule presentation which inclined toward the hydrophilic macromolecule or the hydrophobic macromolecule, and adsorbent [of endotoxin] falls (2+(B-X) 2+(C-X) 2). Moreover, that the value of this formula is 0.5 or less has compactness with the whole moderate film, and it can prevent endotoxin by the whole film. The value of a desirable formula is 0.4 or less. In addition, the distribution condition of the hydrophilic macromolecule of (an internal surface, an outside surface, and pars intermedia) is shown, a hydrophilic macromolecule is distributed at least over each part by at least membranous each part at homogeneity, so that the value of this formula is small, this formula shows that that content is also fixed, distribution of the hydrophilic macromolecule like each part is so uneven that the value of this formula is large, and it is shown that a big difference is in the content of the hydrophilic macromolecule like each part. Henceforth, let the value of this formula be a hydrophilic macromolecule distribution number.
[0034] In addition, the content of the hydrophilic macromolecule like membranous each part can be evaluated from various energy and molecular vibration analysis based on the surface analysis technique. In this invention, the content of the hydrophilic giant molecule of an about [each part] is measured from the ratio of the band strength originating in the hydrophilic giant molecule contained in a membranous internal surface, pars intermedia, and an outside surface by micro Fourier transform infrared spectrophotometry, and a hydrophobic giant molecule. The detail of a measuring method is as given in the column of measurement of the content of the hydrophilic macromolecule like membranous each part.
[0035] When the hollow fiber of this invention observes a membranous cross section with a 300 times as many electron microscope as this, the void accepted clearly or the network structure does not exist. that the void accepted clearly or the network structure does not exist above when observing a membranous cross section with a 300 times as many electron microscope as this is the homogeneity structure where a film internal structure does not have a cavity substantially -- meaning -- ** -- the hollow fiber of this invention becomes possible [preventing migration of the endotoxin from a dialysing fluid side to a blood side by the whole film] by being homogeneity structure like.
[0036] When the hollow fiber of this invention observes a membranous internal surface and a membranous outside surface with a 5000 times as many electron microscope as this, the hole accepted clearly does not exist. If the hole accepted clearly does not exist when observing a membranous internal surface and a membranous outside surface with a 5000 times as many electron microscope as this a membranous surface structure is smooth structure substantially -- meaning -- ** -- the hollow fiber of this invention by being smooth structure like Also when actually processing blood, there is little blinding of a hole, and a secondary polarization layer will also be formed thinly and becomes possible [maintaining the high removal engine performance of unnecessary low-molecular protein, such as beta 2-microglobulin,].
[0037] In addition, generally, evaluation by the scanning electron microscope (SEM) is a stock-in-trade, and membrane structure evaluated membrane structure based on observation by the electron microscope also in this application. In addition, the membrane structure of this invention

is homogeneity and smooth structure substantially as they were explained above. ** -- in order to evaluate homogeneity and smooth nature, it should observe and the electron microscope of the biggest original possible scale factor should estimate, but in order to avoid the effect on the membrane structure by the heat which an electron microscope generates, in the present condition, 5000 times are an upper limit. [like] Therefore, in this application, evaluation of membranous smooth nature was evaluated by observing the internal surface and outside surface of a hollow fiber with a 5000 times as many electron microscope as this. Here, when a hole did not exist and the observation limit in a 5000 times as many enlargement as this sets to 0.2mm, it means that a hole or a cavity 400A or more do not exist.

[0038] Thickness is several micrometers - 80 micrometers, and, as for the hollow fiber of this invention, it is desirable to have the cross section of the perfect circle form where an outer diameter is 100 micrometers - 500 micrometers. As described above, since the hollow fiber of this invention is homogeneity structure substantially, to lower thickness to raising the separation efficiency of a solute is desired, thickness is 15 micrometers - 40 micrometers preferably, and an outer diameter is 200-300 micrometers.

[0039] It is 2 1m by the internal-surface conversion filled up with the hollow fiber of this invention. The sieve multiplier of the beta 2-microglobulin in bovine blood liquid when filtering bovine blood liquid with a protein concentration of 7g [/ml] by part for 200ml/of the rates of flow hematocrit 30% to a module by part for sink and 10ml/of the filtration rates of flow is 50% or more. 50% or less of the elimination factor of beta 2-microglobulin is [a sieve multiplier] insufficient. Moreover, in this invention, the elimination factor at the time of actually pouring blood as mentioned above prescribed the elimination factor of beta 2-microglobulin. This is for forming a secondary polarization layer as mentioned above, and producing a big difference by the sieve multiplier in a drainage system, and the sieve multiplier in a blood system, when blood is actually poured to a hollow fiber.

[0040] Moreover, it is defined as 50% or more of permeability here by the sieve multiplier (SC) shown by the following formula using the liquid which penetrated the liquid supplied to a hollow filament, the passed liquid, and the film, and the beta 2-microglobulin concentration contained in each.

Beta 2-microglobulin concentration T3 in SC(%) =(T1x2)/(T2+T3) x100, however the beta 2-microglobulin concentration T2:supply liquid in T1:permeate liquid: Beta 2-microglobulin concentration in passage liquid [0041] As for the hollow fiber of this invention, it is desirable that membrane structure is held by the film structure-preserving agent. As for a film structure-preserving agent, it is desirable that it is necessary to be the matter easily washed and removed with water, a physiological saline, etc. in case it is used as blood purifier, and it is the water-soluble matter. For example, polyhydric alcohol, such as glycerol and a glycol, polysaccharide, or a surfactant is mentioned. Especially, installation the safety as blood purification film and inside [of polysulfone system homogeneous membrane] pore is especially easy for a glycerol, and is desirable.

[0042] As an approach of creating the hollow filament mold blood purification film of this invention, a hydrophobic macromolecule and a hydrophilic macromolecule are dissolved in the solvent which consists of mixed liquor of a solvent or a solvent, and a poor solvent, for example, a dope undiluted solution is prepared, and the method of making this breathe out from a nozzle and making the film formation by phase separation perform in coagulation liquid is mentioned. By this approach, pore size distribution of membranous pore is narrowed and it becomes possible to acquire the fractionation property of a sharp constituent of blood. Moreover, it is possible by

choosing suitable dope conditions and coagulation conditions to give various solute separation properties to the film.
[0043] Moreover, it is required for formation of a centrum to use a centrum formation heart agent, and this heart agent may be used for coincidence as coagulation liquid. By the film of the conventional polysulfone system, the asymmetric membrane which the film is produced by this technique and the inside solidified densely is formed. Homogeneous membrane can be obtained by using gas or the fluid of low freezing characteristic for a heart agent to it. When gas etc. is furthermore used for a heart agent to what a hydrophilic macromolecule tends to carry out localization to a compact layer in in the case of unsymmetrical structure, a hydrophilic macromolecule can be comparatively introduced into the whole film at homogeneity, and it becomes possible to obtain the film which has the good structure of the balance of a hydrophilic property and hydrophobicity by the whole film.
[0044] The hollow fiber furthermore formed processes rinsing, desiccation, etc. The homogeneous membrane which does not have supporters at this desiccation process has much fall ****** in the membraneous ability which the film contracted with the surface tension of the water accompanying desiccation etc., and was prepared by the phase separation method. In order to prevent this, it is desirable to include a film structure-preserving agent in membrane structure. As for a film structure-preserving agent, being introduced before a desiccation process is optimal after rinsing.
[0045] The hollow filament mold blood purification film of this invention can specifically, for example, as follows, be manufactured.
[0046] The spinning undiluted solution containing 2 - 5 % of the weight of hydrophilic macromolecules, 30 - 60 % of the weight of solvents, and 10 - 50 % of the weight of non-solvents is heated and dissolved in 50-190 degrees C 35% of the weight from the hydrophobic macromolecule 15, and it extrudes from the outside of a double pipe nozzle, and from a center, there is no freezing characteristic to a gas or a spinning undiluted solution, or the low liquid of freezing characteristic is sent in. After it passes through the inside of 40 - 60% of the weight of a glycerol water solution after it was solidified through the 5-60-degree C freezing characteristic liquid after the extruded spinning undiluted solution made it run the 1-20mm air, and it was rinsed, and it infiltrates a glycerol, it is dried with a dryer.
[0047] As the above-mentioned solvent, polar solvents, such as N.N-dimethylformamide, N,N-dimethylacetamide, N-methyl pyrrolidone, and gamma-butyrolactone, can be used by independent or mixing. independent [in ether, such as polyols, such as ethylene glycol, triethylene glycol, a polyethylene glycol, a propanediol, and butanediol, or ethylene glycol monoethyl ether, and diethylene glycol monoethyl ether,] as the above-mentioned non-solvent -- or it can be mixed and used. Moreover, as a hollow formation agent, fats and oils, such as gas, such as nitrogen, an argon, oxygen, carbon dioxide gas, helium, and air, or a liquid paraffin, myristic-acid isopropyl, vegetation, and straight mineral oil, or other low freezing characteristic liquids can be used. The solvent which can be used by this invention, a non-solvent, and a hollow formation agent are not restricted above.
[0048] Hereafter, although an example explains the contents of this invention to a detail further, this invention is not limited at all by the following.
[0049] First, the measuring method of the beta 2-microglobulin of the blood purification film of this invention, endotoxin, an effluent, and a hydrophilic macromolecule content is explained.
[0050] 1. By the internal-surface conversion in which put in the hollow filament of about 10000 SC(%) trial blood purification film of beta 2-microglobulin into the plastic part, and both ends

carried out opening, it is 2 a film area of about 1m. A module is produced. The hematocrit 30% cow fresh blood which carried out anticoagulation processing of this module after washing by the physiological saline and at a blood side (hollow filament inside) is poured by part for 200ml/. By modular internal-surface conversion, it is 2 1m of film surface products. The pump connected to the dialysing fluid side so that it might become a part for filtration velocity/of 10ml of a hit performs hemofiltration, and measurement and the aforementioned SC (%) are calculated about the following. The blood of the inlet port of the module at the time and an outlet and filtrate are sampled for hemofiltration initiation 15 minutes, and the concentration of beta 2-microglobulin is measured with enzyme immunoassay (for example, beta2-MG-EIA TEST Wako Pure Chem industry) etc. In addition, it carries out to the bovine blood liquid used by the measurement concerned by adding the beta 2-microglobulin of the Homo sapiens origin beforehand. According to a formula 1, SC (%) is calculated from the concentration of these beta 2-microglobulin.

[0051] 2. By outside-surface conversion of the hollow fiber for endotoxin adsorption test measurement, it is 2 0.05m of film surface products. A hollow fiber is minced in die length of 1cm, it puts into glassware, and 50ml of endotoxin free water is added, 30ml (about 7.0 EU/ml) of endotoxin solutions is added to the repeat last 3 times, an immersion-decantation is incubated at 37 degrees C for 1 hour, liquid is sampled after that, and the quantum of the endotoxin is carried out. It carries out to measurement of endotoxin by the colorimetry method (Seikagaku TOKISHI color system). (Limit of detection is 0.2 EU/ml) In addition, all of the glass instrument used in this experiment, scissors, etc. use what gave 260-degree-C dry sterilization beforehand, and measurement is carried out by the clean bench.

[0052] Moreover, endotoxin removal with a module is measured by the following approaches.

[0053] 3. An endotoxin radiographic examination evaluation sample uses the same dialyzer as the above-mentioned SC (%) evaluation, and fully washes a module and the whole connection circuit by the single pass using ultrapure water (the Millipore Corp. make, milli-Q system) first. Subsequently, the liquid which flows the blood side (hollow filament inside) of a dialyzer is made into the circulatory system, and it passes by part for 200ml/(total amount of 2l. of circulating water). Circulation liquid is sampled at this time and it asks for early endotoxin concentration. Moreover, a dialyzer with a sink and a UFR controller (the Nipro make, NCU-6) is used for endotoxin content liquid (mixed water of a city water and RO water; about 2.0 EU/ml) according to a counterflow by part for 500ml/at a single pass, and the amount of water penetration between film is turned on the dialysis side to coincidence about 0. Circulating water by the side of after [2 hour progress] blood is sampled. Sampling liquid measures endotoxin concentration similarly by the aforementioned technique. The dynamic range of radiographic examination measurement of endotoxin was carried out by 0.02-0.15EU/ml. Moreover, early endotoxin concentration was below limit of detection.

[0054] 4. Measure with the ultraviolet absorption spectrum (UV) of an extract based on an eluting material test artificial-kidney acknowledgement benchmark test (Japanese artificial organ industrial association). UV of an acceptance standard is 0.1 or less.

[0055] 5. Although the content of the measurement hydrophilic-property macromolecule of the content of the hydrophilic macromolecule of the whole film and a hydrophobic macromolecule is almost the same as the preparation ratio of a spinning undiluted solution or became some fall in this invention, the check of the abundance ratio after hollow filament formation was performed by the following approaches. The KBr tablet after dissolving in a suitable solvent at homogeneity is made to apply and dry a hollow filament, and Transparency IR is measured. This estimates the

peak intensity ratio of the hydrophilic macromolecule origin of IR band, and the hydrophobic macromolecule origin. The compounding ratio (% of the weight) of a hydrophilic macromolecule and a hydrophobic macromolecule measures similarly with a known sample, creates a calibration curve, and, thereby, calculates the content (weight [of a hydrophilic macromolecule] % to an overall-height molecule) of the hydrophilic macromolecule in a hollow filament.

[0056] 6. Assay of the measurement hydrophilic-property macromolecule of the content of the hydrophilic macromolecule like membranous each part measures the front face IR of the inside and an outside about the sample which cut the hollow filament perpendicularly and extended it. Pars intermedia is similarly measured about the sample which shaved off the surface and exposed pars intermedia. Pars intermedia was mostly used as the central part of the thickness section. The front face IR was performed by the FT-IR micro ATR method (IER; diamond). On this condition, about 1.5-micrometer layer on the front face of a sample is measured. Peak intensity was measured similarly and it asked for the intensity ratio. However, in this case, since the estimate of the content by calibration-curve creation was difficult, it estimated the content of a membranous internal surface, an outside surface, and the hydrophilic macromolecule in pars intermedia from the ratio of the peak intensity ratio itself. Since a **** bee and this intensity ratio expressed the content by which the hydrophilic macromolecule like each part and the hydrophobic macromolecule were standardized, they computed the membranous hydrophilic macromolecule distribution number using this value.

[0057] Polyether sulphone 22 % of the weight, 3.0 % of the weight (K-90) of polyvinyl pyrrolidones, (Example 1) A N-methyl-2-pyrrolidone as a solvent the solution which carried out the heating dissolution of the raw material with which polyethylene-glycol #200 consist of 37.5 % of the weight at 120 degrees C as a non-solvent 37.5% of the weight Nitrogen is sent in and it considers as the shape of a hollow filament, and water, a N-methyl-2-pyrrolidone, and polyethylene-glycol #200 passed the inside of the freezing characteristic liquid with a temperature of 40 degrees C which mixes and changes by the weight ratio of 60:20:20, and made it to extrude from the outside of a double pipe nozzle and solidify from a core. Then, rinsed, after infiltrating 50% of the weight of a glycerol, it was made to dry with a dryer, and the bore of 201 micrometers and the hollow fiber of 28 micrometers of thickness were obtained. The void from a 300 time SEM image or the network structure of the cross section of the obtained hollow filament is not observed, but the hole from a 5000 time SEM image on the front face of inside and outside is checked, and it is **********. The content of the hydrophilic macromolecule from IR analysis was about 12%. The intensity ratio of an inside, a middle lamella, and an outside hydrophilic macromolecule was an outside > medium-rise > inside, and the distribution number was 0.21. Although this showed drawing 1 , drawing 2 , and drawing 3 to the example of measurement of a front face IR, it was calculated from the intensity ratio (A1670/A1570) of carbonyl absorption of the polyvinyl pyrrolidone of 1670cm-1, and absorption of the aromatic series of the polyether sulphone of 1570cm-1. In the following examples and examples of a comparison, it measured similarly. SC (%) of the beta 2-microglobulin of this hollow filament was 73%, and in an endotoxin adsorption test, the endotoxin concentration by the side of blood of the endotoxin concentration of the liquid after immersion is below limit of detection below limit of detection, and, as for most invasion by the side of the blood of endotoxin, it did not have an endotoxin radiographic examination in a module, either. Moreover, the eluting material test passed with UV=0.04.

[0058] Polyether sulphone 21 % of the weight, 3.5 % of the weight (K-90) of polyvinyl

pyrrolidones, (Example 2) A N-methyl-2-pyrrolidone as a solvent the solution which carried out the heating dissolution of the raw material with which triethylene glycol consists of 37.75 % of the weight at 120 degrees C as a non-solvent 37.75% of the weight Nitrogen is sent in and it considers as the shape of a hollow filament, and water, a N-methyl-2-pyrrolidone, and triethylene glycol passed the inside of the freezing characteristic liquid with a temperature of 40 degrees C which mixes and changes by the weight ratio of 60:20:20, and made it to extrude from the outside of a double pipe nozzle and solidify from a core. Then, rinsed, after infiltrating 50% of the weight of a glycerol, it was made to dry with a dryer, and the bore of 202 micrometers and the hollow fiber of 32 micrometers of thickness were obtained. The void from a 300 time SEM image or the network structure of the cross section of the obtained hollow filament is not observed, but the hole from a 5000 time SEM image on the front face of inside and outside is checked, and it is **********. The content of the hydrophilic macromolecule from IR analysis was about 14%. The intensity ratio of an inside, a middle lamella, and an outside hydrophilic macromolecule was an outside > medium-rise > inside, and the distribution number was 0.11. SC (%) of the beta 2-microglobulin of this hollow filament was 75%. In the endotoxin adsorption test, the endotoxin concentration of the liquid after immersion is 0.5 EU/ml, and adsorption was seen. The endotoxin concentration by the side of blood is below limit of detection, and most invasion by the side of the blood of endotoxin did not have an endotoxin removal trial with a module, either. Moreover, the eluting material test passed with UV=0.08.

[0059] Polyether sulphone 27 % of the weight, 1.0 % of the weight (K-90) of polyvinyl pyrrolidones, (Example 1 of a comparison) A N-methyl-2-pyrrolidone as a solvent the solution which carried out the heating dissolution of the raw material with which polyethylene-glycol #200 consist of 36.0 % of the weight at 120 degrees C as a non-solvent 36.0% of the weight Nitrogen is sent in and it considers as the shape of a hollow filament, and water, a N-methyl-2-pyrrolidone, and polyethylene-glycol #200 passed the inside of the freezing characteristic liquid with a temperature of 40 degrees C which mixes and changes by the weight ratio of 60:20:20, and made it to extrude from the outside of a double pipe nozzle and solidify from a core. Then, rinsed, after infiltrating 50% of the weight of a glycerol, it was made to dry with a dryer, and the bore of 201 micrometers and the hollow fiber of 28 micrometers of thickness were obtained. The void from a 300 time SEM image or the network structure of the cross section of the obtained hollow filament is not observed, but the hole from a 5000 time SEM image on the front face of inside and outside is checked, and it is **********. The content of the hydrophilic macromolecule from IR analysis was about 3.5%. The intensity ratio of an inside, a middle lamella, and an outside hydrophilic macromolecule was an outside > medium-rise = inside, and the distribution number was 0.14. SC (%) of the beta 2-microglobulin of this hollow filament is 25%, and did not satisfy the requirements for HPM. In the endotoxin adsorption test, the endotoxin concentration of the liquid after immersion is 0.2 or less EU/ml, and adsorption was seen. The endotoxin concentration by the side of blood is below limit of detection, and most invasion by the side of the blood of endotoxin did not have an endotoxin removal trial with a module, either. Moreover, the eluting material test passed with UV=0.02.

[0060] Polyether sulphone 25 % of the weight, 5.0 % of the weight (K-90) of polyvinyl pyrrolidones, (Example 2 of a comparison) A N-methyl-2-pyrrolidone as a solvent the solution which carried out the heating dissolution of the raw material with which polyethylene-glycol #200 consist of 35.0 % of the weight at 120 degrees C as a non-solvent 35.0% of the weight It extrudes from the outside of a double pipe nozzle. From a core Pour water, a N-methyl-2-pyrrolidone, and the liquid of freezing characteristic with which polyethylene-glycol #200 mix

and change by the weight ratio of 60:20:20, and it considers as the shape of a hollow filament. Water, a N-methyl-2-pyrrolidone, and polyethylene-glycol #200 passed the inside of the freezing characteristic liquid with a temperature of 40 degrees C which mixes and changes by the weight ratio of 60:20:20, and made it solidify. Then, rinsed, after infiltrating 50% of the weight of a glycerol, it was made to dry with a dryer, and the bore of 201 micrometers and the hollow fiber of 40 micrometers of thickness were obtained. The network structure from a 300 time SEM image of the cross section of the obtained hollow filament was observed, and the hole from a 5000 time SEM image of an outside surface was checked, and it was not homogeneous membrane but asymmetric membrane. The content of the hydrophilic macromolecule from IR analysis was 5.0%. The intensity ratio of an inside, a middle lamella, and an outside hydrophilic macromolecule was an outside < medium-rise < inside, and the distribution number was 0.74. SC (%) of the beta 2-microglobulin of this hollow filament is 45%, and did not satisfy the requirements for HPM. In the endotoxin adsorption test, the endotoxin concentration of the liquid after immersion is 2.5 EU/ml, and adsorption was seen. In the endotoxin removal trial with a module, the endotoxin concentration by the side of blood is 0.15 or more EU/ml, and the invasion by the side of the blood of endotoxin was seen. Moreover, eluting material tests were UV=0.11 and a rejection.

[0061]

[Table 1]

	実施例１	実施例２	比較例１	比較例２
高分子の素材	ＰＥＳ ＰＶＰ	ＰＥＳ ＰＶＰ	ＰＥＳ ＰＶＰ	ＰＥＳ ＰＶＰ
膜構造保持剤	ｸﾞﾘｾﾘﾝ	ｸﾞﾘｾﾘﾝ	ｸﾞﾘｾﾘﾝ	ｸﾞﾘｾﾘﾝ
内径（μｍ）	２０１	２０２	２０１	２０１
膜厚（μｍ）	２８	３２	２８	４０
親水性高分子含有率 膜全体	１２％	１４％	３．５％	５％
親水性高分子分布比	０．２１	０．１１	０．１４	０．７４
規格化　内表面	０．３５	０．４８	０．１１	０．２３
含有率　外表面	０．４７	０．５６	０．１３	０．０８
(ﾋﾟｰｸ強度比)中間部	０．４４	０．５３	０．１１	０．１３
膜断面構造	均一	均一	均一	非均一
膜内表面構造	平滑	平滑	平滑	平滑
膜外表面構造	平滑	平滑	平滑	多孔質
β2-ＭＧ篩い係数	７３％	７５％	２５％	４５％
ＥＴ試験(EU/ml)	ＮＤ	ＮＤ	ＮＤ	≧0.15
溶出物試験	０．０４	０．０８	０．０２	０．１１

（注）ＰＥＳ：ポリエーテルスルホン
ＰＶＰ：ポリビニルピロリドン
ＮＤ：検出限度以下(Not detect)

DESCRIPTION OF DRAWINGS

[Brief Description of the Drawings]

[Drawing 1] It is the IR spectrum of the internal surface of the hollow fiber of this application example 1.

[Drawing 2] It is the IR spectrum of the outside surface of the hollow fiber of this application example 1.

[Drawing 3] It is the IR spectrum of the cross section of the hollow fiber of this application example 1.

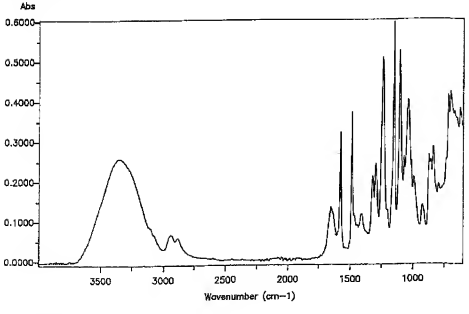
[Drawing 4] It is a 5000 times as many electron microscope photograph as the internal surface of the hollow fiber of this application example 1.

[Drawing 5] It is a 5000 times as many electron microscope photograph as the outside surface of the hollow fiber of this application example 1.

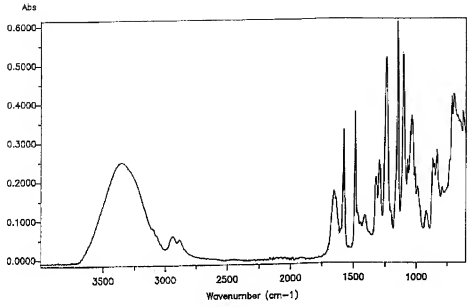
[Drawing 6] It is a 300 times as many electron microscope photograph as the cross section of the hollow fiber of this application example 1.

DRAWINGS

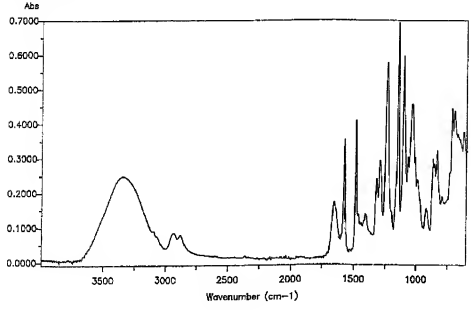
[Drawing 1]



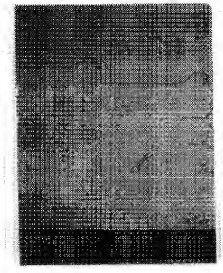
[Drawing 2]



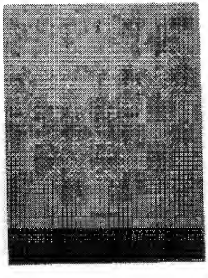
[Drawing 3]



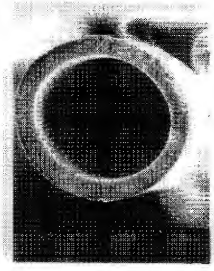
[Drawing 4]



[Drawing 5]



[Drawing 6]



[Translation done.]